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VOLUME XV, 1940

ISSUED BY THE BRITISH MEDICAL ASSOCIATION

London: British Medical Association House
Tavistock Square, W.C.1

SOYA BEAN FLOUR WITH DRIED MILK

A CHEAP AND EFFICIENT SUBSTITUTE FOR BREAST MILK

BY

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In many countries of the world the alternative to breast-milk feeding is usually the early demise of the infant. To this various factors undoubtedly contribute, but for immense numbers the primary factor is the absence or prohibitive cost of any adequate substitute for breast-milk. Fluid cow's milk is unobtainable throughout the vast tsetse-fly areas of Africa, and its prohibitive cost or scarcity place it beyond the reach of millions in India, China and other Asiatic countries ; moreover, dairy milk supplies may often fail in time of war. Even if obtainable, the excellence of fluid milk as a culture medium is fraught with danger to infants whose mothers are unable, whether owing to poverty or ignorance, to keep it under proper hygienic conditions. In London dried milk has, to a great extent, replaced fluid dairy milk as the basis for the artificial feeding of infants, to the great advantage of babies living in families in which there is considerable risk of food contamination. In Great Britain its cost to the working-class mother, who gets it from a welfare centre, is about the same as that of an equivalent amount of dairy milk, and to the necessitous it can be supplied free. In this respect members of the professional classes and others who are obliged to buy it from a chemist are heavily penalized, since its cost is often beyond their means. In any case, full-cream dried milk cannot be supplied at a cost which would make possible its general use among the native populations of Africa or in India and other Eastern countries.

Soya bean is a cheap foodstuff with many valuable qualities. The investigation here described is a comparison of the health and development of a number of infants, living in their own homes, who were given a mixture of equal parts of dried milk and soya bean flour, together with certain supplements, and of a control series given dried milk, the same supplements and also added iron. That is, the well-being of infants on the mixture of dried milk and soya was compared with that of another group of infants on the optimum artificial diet the author could devise. A mixture of equal parts of dried milk and soya bean flour could be sold for little more than half the price of dried milk alone. If costs of distribution could be cut down, this would bring it within the means of many mothers unable at present to buy dried milk, although

its price would unfortunately still remain too high for great numbers of people in India and other Eastern countries.

One of the important defects of cow's milk as a food for infants is its low iron content. Soya bean is said to be a popular remedy for anaemia in China (Adolph and Kao, 1932), and its iron content is fairly high. It was therefore hoped that a mixture of milk and soya bean would prevent the iron deficiency anaemia, and consequent lowered resistance to infection (Mackay and Goodfellow, 1931), which is so common in babies in every country where this problem has been investigated.

Types of soya bean flour

The legume soya bean contains little or no starch when ripe. Moreover, it contains much more protein than carbohydrate and a high percentage of fat (Bailey, Capen and Le Clerc, 1935 ; Horvath, 1938). Its use as a human foodstuff has been limited in most countries by its unpleasantly bitter taste, which can, however, be removed by certain processes of treatment (Bailey, Capen, and Le Clerc, 1935). In China, where it is a staple foodstuff, soya is used in a great many different forms, known in the literature as soymilk, soycheese, soycurd ; it is also used in a variety of sauces, as bean sprouts, and as roasted and salted beans (Miller and Wen, 1936). Fermentation plays a large part in the preparation, and may, it is said, extend over years. The composition even of two products known by the same name appears often to vary widely : soya bean curd, for example, may contain 8 per cent., 17 per cent., or 58 per cent. protein, according to whether it is ' fresh,' ' smoked ' or ' frozen ' (Horvath, 1938) ; and this difficulty of distinguishing between or assessing the composition or food value of the various preparations (including the flours) referred to in the literature is, for the ordinary reader, considerable.

Before describing the details of this investigation, some mention of the different varieties of soya bean flour may therefore be helpful, for medical readers in this country are not likely to be versed in these technicalities. If contributions on the experimental use of soya bean in human nutrition are consulted, references are found to flour made from heated beans, from unheated beans, from whole beans, and from pressed cake (i.e. the residue after extraction of oil) ; mention is also made of hydraulic meal, expeller meal, flour made by wet-grinding and flour made by dry-grinding, and to ' soy-milk powders.' The following summary of the main types of flour which have been used for feeding babies may be of assistance to other physicians wishing to employ the bean :

(a) The dry-ground flour from the whole unheated bean has a bitter taste, and the fat turns rancid with keeping, which greatly restricts its use. As will be shown later, experiments on rats have demonstrated that this unheated protein is not easily utilized (Osborne and Mendel, 1917) and the carbohydrates of the uncooked flour are digested with difficulty (Adolph and Kao, 1932). The composition of the whole bean shows considerable variation, depending both on the variety of the plant and on its conditions of growth (Horvath, 1938).

(b) Commercial soya flour is largely prepared from the residue left after extraction of the fat, the fat being used for many purposes. This flour (sometimes called ' oil meal,' ' expeller meal ' or ' hydraulic meal ') has lost most of its fat, and consequently presumably most of its vitamin A and D, and is in this respect a less valuable foodstuff. On the other hand, in the process of oil extraction the material may be raised to a high temperature, which increases the nutritive value of the protein (Hayward, Steenbock and Böhstedt, 1936).

Various processes are used for such oil extraction, known as ' expeller,' ' hydraulic ' and ' solvent ' processes. The nutritive value of the protein (Hayward, Steenbock and Böhstedt, 1936), the quantity of fat remaining and the amount of ash (Bailey, Capen and Le Clerc, 1935 ; Horvath, 1938) vary widely. According to Guy and Yeh (1938b), ' most of the soya bean flours on the American market are made from the residue or ' pressed cake ' left after high-temperature extraction of oil from the bean. This flour is brown as a result of heating, and the nutritive value of its protein is good.

(c) ' Wet grinding ' of the bean has been used by Chinese physicians on a small scale and by some American physicians (Tso, 1928 ; Guy and Yeh, 1938a ; Rittinger and Dembo, 1932). This method, it is said, ' brings a certain amount of the protein into fine suspension and leaves the cellulose in the bulky residue which is filtered off ' (Guy and Yeh, 1938a). The composition of a ' soy milk ' made by this method varies widely, especially as regards protein and phosphorus content, the composition depending on the amount of boiling, stirring and evaporation. Guy and Yeh say that this soya milk ' is sold hot in Peking by street vendors, and taken by old people in place of tea. Contrary to some Western notions, it has not been usual, at least in the North (of China), to feed it to infants.' Horvath (1938) states that a wet-process flour has ample chance of turning rancid, which is a serious disadvantage, since rancidity causes destruction of vitamin A and D and the formation of toxic products.

(d) Hand-ground flour has been prepared from the roasted whole bean, and its protein should be well utilized, but so far as the author knows, it has only been used on a small scale (Guy and Yeh, 1938b).

(e) Of recent years soya flour has been prepared by the patent Berczeller process (Bailey, Capen and Le Clerc, 1935). This was devised in order to obtain a commercial flour of high fat content and good keeping quality, devoid of the unpleasant strong taste of the bean. The flour used in the present investigation was prepared by a modification of this process and is sold under the proprietary name of soyolk, the makers claiming that the taste is better than that of Berczeller flour. The Berczeller process is described by Bailey, Capen and Le Clerc as follows : the beans are cleaned, subjected to the action of saturated steam for ten to fifteen minutes, dried and cracked to remove the husks. The germ is removed in this process. The flour is subjected to steam distillation, which removes some of the volatile material responsible for the bitter taste. Soyolk is a fine, cream-coloured powder with very little taste, and what taste it has has been described as neutral. No chemicals are used in its preparation. The makers claim that the protein is of high biological value, but, so far as the author is aware, this has not been investigated by feeding experiments either with soyolk or with Berczeller process flour. The flour can be kept for long periods without turning rancid. Several other patented processes for obtaining a flour with a high fat content which does not turn rancid are given by Bailey, Capen and Le Clerc (1935).

(f) There are also on the market so-called ' soy-bean-milk powders,' preparations of soya flour mixed with other substances, with the object of rendering them suitable for infant feeding. For example, the flour from pressed cake has been marketed in America with additions of cereal, oil and minerals (Hill and Stuart, 1929), but this flour is apparently deficient in vitamin A. Blackfan and Wolbach (1933) recorded the appearance of keratomalacia in a baby fed on such a ' soy milk.'

From the foregoing it is obvious that when considering reports on the use of soya bean flour in human nutrition it is necessary to keep in mind what type of flour was used and whether or not various additions have been made to it in the course of preparation. Even apart from such additions, the differences are wide : the nutritive value of the protein, the percentage present, the amount

of fat and its keeping properties, the digestibility of the carbohydrate, the amount of vitamins present and, not least important, the amount and balance of the mineral elements all vary widely according to the method of preparation.

The composition of soyolk and yolac

The mixture of dried milk and soya flour (soyolk) used in this investigation was given the name of ' yolac.' Yolac was prepared by Messrs. Cow and Gate by mechanical mixing of equal parts by weight of their full-cream dried milk powder and soyolk. An attempt was made in the first instance to incorporate soyolk in fluid milk and then dry the mixture, but as the heat caused chemical changes in the soyolk this method was discarded in favour of mechanical mixing of the two powders.

TABLE I

ANALYSES OF DRIED MILK, SOYA BEAN FLOUR, AND YOLAC

	DRIED MILK	SOYOLK			YOLAC	
	FIRM'S FIGURES A	CRON-SHAW B	KUPEL-WEISER C	WIDDOW-SON D	FROM A and B	WIDDOW-SON
Total nitrogen (gm. per 100 gm.)	—	—	—	6·49	—	5·13
Protein ,,	26·6	44·2	41·5	40·5	35·2	32·2
Fat ,,	27·3 } 91·5	20·6 } 78·9	20·3	19·9 } 81·0	23·9 } 84·9	25·7 } 85·2
Carbohydrate ,,	37·6	14·1	20·0 to 24·8	20·6	25·8	27·3
Water ,,	2·6 } 8·6	11·1 } 14·8	9·0	—	6·8 } 11·6	3·0
Ash ,,	6·0	3·7	—	—	4·8	—
Calcium (mgm. per 100 gm.)	843	—	270	214	—	553
Phosphorus ,,	742	—	—	352	—	500
Phosphoric acid ,,	—	1340	1120	—	—	—
Total iron ,,	—	—	—	16·2	—	9·6
Available iron ,,	—	—	—	13·2	—	8·1
Magnesium ,,	96	—	—	219	—	158
Calorie value (per 100 gm.)	517	431	—	—	474	483
Protein ,,	109	181	—	—	145	132
Fat ,,	254	192	—	—	223	239
Carbohydrate ,,	154	58	—	—	106	112
Calorie value per drachm (60 grains) ..	20·1	16·8	—	—	18·5	18·9

Table 1 gives the composition of the dried milk used (Messrs. Cow and Gate's figures) and the composition of soyolk (two sets of figures supplied by the firm marketing the flour and an analysis kindly carried out by R. A. McCance and E. M. Widdowson) ; and the composition of yolac (as calculated from the figures supplied by the two firms, and from direct analyses by McCance and Widdowson).

The analyses show general agreement. Soyolk contains over 40 per cent.

protein, about 20 per cent. fat and 20 per cent. carbohydrate. It contains about a quarter as much calcium and about half as much phosphorus as dried cow's milk, and about twice as much magnesium and about eight times as much iron. Since soya flour contains less calcium than phosphorus, most workers using soya flour for infant feeding have added a calcium salt in order to augment the calcium intake (Tso, Yee and Chen, 1928 ; Hill and Stuart, 1929 ; Chang and Tso, 1931 ; Rittinger and Dembo, 1932 ; Stearns, 1933 ; Rittinger, Dembo and Torrey, 1935 ; Guy and Yeh, 1938 a, b). Sodium and chlorine content are not given in this table, but these also are low compared with dried milk, and have usually been added to 'soya-milk' for infants.

Yolac was used mixed with water in the proportion of approximately one in eight. In this mixture the percentage of protein is high compared with average cow's milk, and the percentages of fat and carbohydrate are distinctly lower (see table 2). The percentage of iron in yolac is about five times as much as in dried milk (see table 3), the calcium two-thirds as much, the phosphorus two-thirds as much and the magnesium about one-and-a-half times as much (using Messrs. Cow and Gate's figures for the percentages of calcium, phosphorus and magnesium in the dried milk, and Widdowson and McCance's figures for yolac). Therefore in this mixture of soya flour and milk, the quantity of calcium present and the ratio of calcium to phosphorus should be adequate without further adjustments. As cow's milk contains, say, twice as much sodium and chlorine as breast milk (Schall and Heisler, 1917), a mixture of equal parts of dried cow's milk and soyolk would presumably supply ample of these substances for the infant's needs.

TABLE 2

PERCENTAGE OF PROTEIN, FAT, AND CARBOHYDRATE IN YOLAC COMPARED WITH MILK

	DAIRY MILK (HUTCHISON AND MOTTRAM)	DRIED MILK COW AND GATE, 1 IN 8 (FIRM'S FIGURES)	YOLAC, 1 IN 8 (WIDDOWSON)
Protein	3 to 4	3·3	4·0
Fat	3·5 to 4·5	3·4	3·2
Carbohydrate	4 to 5	4·7	3·4
Mineral matters ..	0·7	0·8	0·6*

* Firm's figures.

TABLE 3

IRON IN DRIED MILK AND YOLAC (WIDDOWSON)

	DRIED MILK COW AND GATE	YOLAC
Mgm. per 100 gm.	2·00	9·70
	1·81	10·91
	2·03	9·38
	—	8·37
Average total	1·95	9·59
Average available ..	1·95	8·15
Mgm. per 1 lb.	8·8	43·5

The calorie value of 1 drachm (60 grains) of Cow and Gate full-cream dried milk is approximately 20, and of yolac 19 (see table 1) ; thus the calorie value of a one in eight mixture of yolac is about that of cow's milk. The infants' feeds were prepared by mixing the yolac or dried milk with hot water. The mixture was not boiled after mixing. The bulk of a given weight of yolac was about the same as that of the dried milk used, so the mothers were provided with the Cow and Gate measure for both yolac and dried milk. If allowed to stand the soyolk began gradually to sink to the bottom, but shaking reproduced a satisfactory mixture.

The nutritive value of soya bean flour with special reference to soyolk

Horvath (1938), who is an authority on the soya bean, gives in a recent article an extensive bibliography on the composition and nutritive value of the bean and its use in human nutrition. References are confined in this paper to articles bearing on the use of soya flour for infant feeding which are likely to be accessible to medical readers, but no attempt has been made to cover the whole literature regarding even this limited field.

The main protein of soya bean is a globulin, glycinin. The basic amino acids have been determined by Bruce Jones and Waterman (1921) by the van Slyke method and are set out in their article. The nutritive value of the protein, as determined by the growth of rats, has been examined by Osborne and Mendel (1917), and among other later workers by Hayward, Steenbock and Böhstedt (1936). They found that the raw bean provided an inefficient protein, but that autoclaving the bean (one and a half hours' heating with steam at 17 pounds pressure) or alternatively adding 0·3 per cent. cystin practically doubled the nutritive value of the protein fraction. Dry-heating in the laboratory for one and a half hours failed to improve the nutritive value. They concluded that a high temperature so altered the protein as to cause some essential fraction to become available for absorption and metabolic use. They drew attention to the wide variation in the nutritive value of the protein of different commercial flours. The brown commercial flours, made after the extraction of oil at high temperatures, or flour from the residue of 'solvent' methods of oil extraction were as good a source of protein as the bean autoclaved in the laboratory. The makers of soyolk claim that the protein of this flour is also of high biological value, but whether or not the degree of steam heating they use is sufficient to ensure the maximum nutritive value of the protein does not seem to have been determined.

The carbohydrate of the ripe bean is said to be present in the form of galactans, pentosans and insoluble cellulose, with small amounts of cane sugar and reducing sugar. Estimates of the sugar content vary (Rittinger and Dembo, 1932 ; Bailey, Capen and Le Clerc, 1935 ; Horvath, 1938). One author states that there is as much as 9 per cent. of cane sugar (Ruhräh, 1909). Some starch is present when the bean is not fully ripe. According to different analyses, the fibre content is usually between 2 per cent. and 4 per cent. The flour made from shelled beans contains little cellulose (Ferrée, 1929).

The composition of soya bean fat is discussed by Rittinger and Dembo (1932). They say that it is liquid at room temperature and contains a high percentage of unsaturated acids. The fat of the untreated whole-bean flour quickly turns rancid, and this destroys the vitamins A and E present (Horvath, 1938). The Berczeller process greatly improves the keeping properties of the fat. Soyolk, it is claimed, has been kept satisfactorily for two years in a laboratory ; in any case, during the course of the present work none of the

mothers complained of any rancidity, although, owing to home circumstances, the food was probably often kept in hot rooms. The bean is rich in phosphatides (Horvath, 1938).

The vitamin value of one ounce of the bean is given by Rittinger and Dembo (1932) as follows : vitamin A 560 units ; vitamin D 28 Steenbock units ; vitamin B complex 22 units. Sherman (1937) gives the average vitamin A value of cow's milk as 292 international units per 100 grammes, and, on this basis, a full-cream milk powder, if there were no destruction of vitamin A, would have about 654 units per ounce, as compared with 560 units in the soya bean. The range of values given in the literature for cow's milk is, however, extremely wide, varying from 15 to 700 units per 100 c.c. according to different authors (Willstaedt and With, 1938). The cow's diet plays a large part in determining the vitamin A value of the milk secreted. Sherman considers that such figures give an exaggerated and erroneous idea of its usual variability, which he holds to be fairly small. What the actual variation may be or the degree of error in the various methods of estimation employed it is impossible for the ordinary physician to judge. Wan (1932) compared the vitamin B content of dried milk and soya bean, and arrived at the conclusion that soya bean contained two-thirds as much B_2 and three times as much B_1 as the full-cream dried milk, klim, with which he compared it. The bean also contains vitamin E (Horvath, 1938) and vitamin K (Dam, 1935).

The iron content of soya bean is high. According to Widdowson's figures (see table 3), it contained about eight times as much as the dried milk with which it was compared, and most of this iron is in the so-called available form. Adolph and Kao (1932) state that soya bean cheese or curd is regarded by the Chinese as a cure for anaemia, and they cured rats of ' milk anaemia ' by feeding them on the whole soya bean which had been ground and cooked.

As already pointed out, soyolk contains less than two-thirds as much calcium as phosphorus, whereas cow's milk contains more calcium than phosphorus. The calcium-phosphorus ratio is of importance because a relative deficiency of calcium would predispose to rickets and tetany. The mixture of dried milk with soyolk should, however, supply a safe calcium-phosphorus ratio. Horvath (1938) states that some workers investigating metabolism on soya bean diets have upset the metabolism of calcium by adding fat to the soya bean, which is already rich in fat, and that poor calcium retention has been due to excess of fat. Adolph and Shen (1932) have shown that calcium is well-utilized by adults on soya bean diets and point out that the bean is an important source of calcium for the Chinese.

The use of soya bean in feeding infants and children

During the last thirty years reports have appeared on the use of various ' soya milks ' for feeding infants and young children. In 1909 Ruhräh, the pioneer in this work, used gruels made from boiled beans (1909a), and from dry-ground flour with added sugar (1909b), as a temporary diet for babies with and without summer diarrhoea, for marasmic infants and for subnormal children. He gives few details, but was apparently satisfied with his results. He has also given soya gruel with barley flour, salt and condensed milk, (Ruhräh, 1915). Sinclair (1916), using for short periods a similar gruel from dry-ground flour without added sugar for seventy-four cases of diarrhoea under three years old, states that forty-four did well.

Hill and Stuart (1929) used a flour from pressed cake (i.e. the residue from soya bean after extraction of oil), to which were added barley flour, olive oil, sodium chloride and calcium carbonate, the mixture going under the name of sobee. They say that about forty infants took it well and thrived. Stearns

(1933), who investigated the nitrogen, calcium and phosphorus metabolism of two children on such a mixture, considered the retention of calcium and phosphorus unsatisfactory, but found the relative retentions of nitrogen, calcium and phosphorus improved by substituting dicalcium phosphate for calcium carbonate. Moreover, this 'soy milk powder' is also deficient in vitamin A, for, as already mentioned, Blackfan and Wolbach (1933) have recorded the development of keratomalacia in a six-month-old infant fed on it.

The largest series of cases yet published are those of Rittinger with his associates Dembo (1932) and Torrey (1935), who have given soya milk to 205 infants. They gave at first a wet-ground flour, with added sugar, fats and minerals. The majority of babies gained well, and had three to four large green soft stools daily. Some with six or seven stools daily did not thrive. The stools improved if the mixture was well boiled. Nevertheless with a wet-ground flour which may turn rancid, causing destruction of vitamin A and vitamin E, there is presumably considerable risk of symptoms of vitamin A deficiency developing (Horvath, 1938). As already pointed out, the composition of wet-ground flour varies widely with the details of preparation. Later, Rittinger and his colleagues (1935), used a dry-ground flour with or without partial breast feeding, adding more carbohydrate than in their earlier work. The infant's weight curves paralleled the Holt line for the most part, but the majority were below it. Adding skimmed milk and wheat germ to the diet improved growth. They carried out x-ray and biochemical investigations, and blood counts in some cases, with normal results in nearly all instances.

In China, Tso and his associates (1928, 1931) used a wet-ground flour, with additions of sodium chloride, sugar and other substances, and carried out various metabolic studies on infants. They concluded that calcium is inadequate in such 'milk' (Tso, Yee and Chen, 1928), and that in order to furnish sufficient protein 18 per cent. of the total calorie intake should be provided by the protein (Tso and Chu, 1931). Chang and Tso (1931) suggest the use of a wet-ground flour with added sugar, dried by a spray process, to which is added before use more sugar and calcium lactate, sodium chloride, cod-liver oil and cabbage water. Following this work, a wet-ground flour, prepared at the local health station, was used in Peiping by Guy and Yeh (1938a), because of the urgent need of an artificial food cheaper than cow's milk. They too made various additions to the flour (sugar, starch, calcium lactate, sodium chloride). They used this 'soymilk' as a supplement to breast feeding, giving, like Chang and Tso, cod-liver oil and cabbage soup to supply vitamins D and C. They found that the babies had less muscular vigour than the breast-fed ones and were subnormal in weight. They concluded that this method of preparation was cumbersome and impractical for their purpose. Later they fed forty-nine babies on a similar mixture but used a hand-ground flour made from roasted beans (1938b). They considered these results satisfactory in spite of a few failures.

Reid (1935) after satisfactory tests on young rats and puppies of soya flour (Berczeller process) with egg yolk, sugar, peanut oil, calcium lactate and sodium chloride, suggested its use for infants. Such a powder could hardly be supplied at a low cost, and Horvath (1938) says the egg yolk is subject to deterioration in such blends and adds unnecessarily oil and phosphatides to soya flour which is already rich in these substances.

Soy milk has been suggested for the treatment of babies with eczema (Hill and Stuart, 1929 ; Becker, 1934 ; Klein, 1933). The theoretical grounds for its use put forward by different workers are that the eczema may be due to milk sensitization, or that the bases present in soya bean or alternatively its unsaturated fatty acids may be beneficial. Because a soya bean diet renders the urine alkaline, it has been used for the treatment of urinary infection

with b.coli (Mader, 1932), but with the drugs now available soya flour is unlikely to be employed.

Soy milk has been used for the treatment of diarrhoea, and the Dionne quintuplets were given ' soy acidophilus milk ' (Horvath, 1938).

Caldwell (1933) in New York used soya bean flour (prepared by the Berczeller process), combined with other foodstuffs, as a supplement to the diets of sixty-six young children in poor economic circumstances. The average increase in weight of the soya group was distinctly superior to that of fifty controls, but few details are given. Aykroyd and Krishnan (1937) used cooked soya bean as a supplement to the diet of school-children in Southern India with little benefit, though the children's diets were defective in various respects, as proved by the marked benefit to growth and general health which resulted from a supplement of skimmed milk. They conclude that the soya bean does not make good the particular deficiencies common in these diets.

To summarize, no authors have published any detailed statistical results whereby the progress of babies given soya preparations can be compared with that of similar babies living under similar conditions but given preparations of cow's milk. Judging by the statements and conclusions of the authors quoted above, it seems, as might be expected, that babies fed on soya flours without any admixture of cow's milk do not, on the whole, make as good progress as babies having milk as the basis of their diet.

Horvath (1938) quotes the following sentences from a recent publication of the Food Research Division of the U.S. Department of Agriculture : ' The most expensive food constituents are minerals, vitamins, proteins and fats. Soy bean flour is rich in all these food constituents and yet relatively cheap.' It is, in fact, one of the cheapest sources of protein and calcium (Bailey, Capen and Le Clerc, 1935). It is hoped that the investigation here described may encourage the large-scale use in infant feeding of a mixture of milk with this cheap foodstuff in those parts of the world where a sufficiency of milk alone is beyond the means of the people.

Nature of present investigation

The present investigation was carried out in the out-patient department of the Queen's Hospital for Children from August, 1935, to March, 1938, the babies concerned living in their own homes. They were divided into three groups. One group was given a mixture of equal parts of dried milk and soya bean, which the makers have called yolac ; the other two groups were given dried milk with added iron. (A few babies in each group received some breast milk, usually only for a short period after inclusion in the investigation.) The progress of the latter two groups, which differed only in their vitamin A intake, was so similar (Mackay, 1939) that, except when otherwise stated, they will together be regarded as the control group. It can safely be assumed that both these control groups had sufficient vitamin A.

Group 1 received yolac (i.e. dried milk plus soya bean), sugar, orange juice and cod-liver oil emulsion. Of the two control groups, group 2 received dried milk with added iron, sugar, orange juice and cod-liver oil emulsion ; and group 3 received dried milk with added iron (called hemolac), sugar,

orange juice and a vitamin D emulsion. From six months old, in addition to yolac or hemolac, all children received table food.

Full records were kept of the clinical condition of the babies, together with any complaints by the mothers of fretfulness, crying, failure to take the feeds, or other feeding difficulties, and the presence of constipation or looseness of the bowels was carefully noted. The results have been analysed, and objective results and subjective impressions resulting from this comparison are set out in this paper.

Clinical material. NUMBER OF BABIES. A total of 225 babies were taken for the purpose of this investigation, but only 150 were available for the final statistical comparison. Of these 150, 48 were yolac cases and 102 were controls, 49 of the latter getting iron-containing dried milk with cod-liver oil, and 53 the same dried milk and iron with vitamin D and no supplement of vitamin A. An analysis of the reasons for the exclusion of 75 cases is given under the heading of results.

AGE OF INFANTS. Of the 150 children included in the final comparison, the ages when first seen were as follows : Under one month, 13 cases (8·7 per cent.) ; one to two months old, 46 cases (30·7 per cent.) ; two to three months old, 54 cases (36·0 per cent.) ; three to four months old, 34 cases (22·7 per cent.) ; four to five months, 3 cases (2·0 per cent.). Hence over three-fourths of the children were under three months old when first seen.

DURATION OF ATTENDANCE AND FREQUENCY OF ATTENDANCE. No child was included who did not attend and receive yolac or iron-containing dried milk for over four weeks. The period of attendance varied from thirty-five days to twenty-six months, and averaged nine months. Mothers were asked to bring their babies up to the hospital at first twice or once in the week, and when established on their diet at fortnightly intervals. Many were seen fortnightly with great regularity. They were examined naked by the author. Any child who was not seen at these clinics for a period of six weeks, even though taking the food prescribed, was reckoned as having ceased to attend.

CLINICAL CONDITION OF INFANTS. As it was decided to test yolac both as regards its tolerance by infants in varying health and its suitability in other respects, infants brought up to hospital for a variety of complaints were included in the investigation, and many of these babies had suffered from feeding upsets and from infections before they were seen. The majority were under normal weight when first included and a few were emaciated or in very poor condition. The average birth weight, as given by the mothers, was 7 pounds 0·8 ounces.

ECONOMIC STATUS OF FAMILIES. Many of the parents were in poor circumstances (e.g. the father was a casual manual worker or unemployed and was often receiving a milk grant or other help from public or charitable sources), but some were in much better circumstances, e.g. small traders, policemen, and others in regular work.

The diet given. As a jumping-off ground, most babies at their first attendance were put on to a full-cream dried milk. A few babies in each group received some breast milk. During the second week of attendance they were gradually changed from the unmedicated dried milk to either yolac

or iron-containing dried milk, approximately half a drachm of the new food being substituted daily. Thus to change a baby from three drachms per feed of unmedicated dried milk to three drachms per feed of yolac or iron-containing dried milk would take six days. In the same way, a week was usually taken to work up to the full dose of cod-liver oil or vitamin D emulsion. The same principles of feeding were applied to all the babies, whatever the group : the same additions of sugar were given, together with a supplement of orange juice and cod-liver oil (or vitamin D for those in group 3), the only difference being that the yolac group received yolac and the controls iron-containing dried milk. From about six months old, mixed food was started, and the yolac or hemolac correspondingly reduced, so that by about seven months old the baby instead of getting about one-and-three-quarters or two pounds in the week (providing about one litre daily), received about one to one-and-a-quarter pounds each week (providing say one pint or a little over half a litre daily), with the gradual addition of fish, eggs, puddings (usually made from dairy milk), vegetables and fruit. Meat was usually given before ten months old.

HEMOLAC. The dried milk (hemolac) used was a full-cream, roller-process milk, in which iron and ammonium citrate had been incorporated before drying in the proportion of 31½ grains to the pound. This quantity is sufficient to prevent nutritional anaemia. The mothers were asked to obtain the milk from the hospital, where it was sold to them at cost price or exchanged for any other dried milk given by the borough to a necessitous mother. A considerable number of mothers obtained hemolac from their welfare centres, in which case it was not possible to check the mother's account of the amount given to the baby by the record of the amount sold. At about six months old most babies were receiving the equivalent of say one-and-three-quarter pints (about one litre) of dairy milk daily. After seven months the hemolac allowance was generally the equivalent of about one pint daily of dairy milk, but in addition many babies received not infrequently milk pudding made from dairy milk, and this might account for another quarter of a pint of milk daily.

YOLAC. The composition of the yolac has already been discussed. It was used in the same quantities as the hemolac and in similar dilution. After six months old these babies, like the controls, were given milk puddings made with dairy milk.

SUGAR. Usually 1½ drachms (say 6 grammes) of castor or granulated sugar was added to each feed of hemolac or yolac. The calories in added sugar varied between 60 and 135 in the day.

VITAMIN C. Mothers were advised to give their babies not less than one teaspoonful of orange juice daily. Much larger quantities were often given, especially to constipated babies, and as there was less constipation in the yolac group these babies received less orange juice than the controls. From six months old various fruits and vegetables were included in the diet.

VITAMINS A AND D. Babies of groups 1 and 2 were ordered cod-liver oil emulsion, 3 drachms (say 11·5 c.c.) daily of a 50 per cent. emulsion, providing them with 1½ drachms (nearly 6 c.c.) of cod-liver oil daily, say 580–870 international units of vitamin D and 4600–7000 international units of vitamin A (determined by the spectrophotometer). The oil was bought from Messrs. Allen and Hanbury, and these values have kindly been supplied by Mr. Norman Evers. Babies of group 3 were ordered an emulsion of vitamin D (calciferol) providing them with say 1575 international units daily. It has been shown elsewhere (Mackay, 1939) that babies of group 2 and 3 were similar in rate of

gain in weight, general morbidity rates, incidence of infections of eyes and of mouth, incidence of lesions of the skin (whether infectious or non-infectious), and in skin texture. Hence it has been assumed that they received their full requirements of vitamin A ; and groups 2 and 3 have, therefore, been amalgamated to form a larger control group. As already stated, the quantity of vitamin A and carotene in soya bean is said to be of the same order as would be present in dried milk if no destruction occurred during the process of drying.

Results

The general progress of most babies in both yolac and control groups was good. Previously when the author has had under observation a group of babies receiving extra iron with their milk and another group getting no extra iron, babies of the latter group have looked definitely inferior (Mackay and Goodfellow, 1931). As a group the yolac babies did not look inferior to the hemolac babies, and so by inference they looked better than babies fed on cow's milk without extra iron. Below are analysed, first, the findings regarding the 150 children finally included in this investigation and, secondly, the information available regarding the 75 children excluded from the statistical comparison, since it is necessary to consider whether any children were excluded because they did not tolerate the food given them.

The 150 babies finally included in the comparison. At the beginning of the observation the yolac group and the controls were fairly evenly matched (see table 4). The average age tallied to within one day, the average weight differed by about one ounce and the balance of sexes was similar : in the yolac group 56 per cent. were males, in the control group 61 per cent. The average birth weight, as given by the mother, was 7 pounds 1·1 ounces for yolac cases, and 7 pounds 0·7 ounces for controls. The average period of attendance was, however, nineteen days longer in the yolac group, the latter averaging nineteen days older at the end of the observation. Yolac babies attended for an average period of 9 months 12·6 days ; controls for 8 months 23·6 days. The average time from the first attendance taken to change the babies completely on to a diet of yolac was eighteen days, and on to hemolac fifteen days. The change was begun about one week after the first attendance. The babies getting some breast milk, of which there were a few in each group, are excluded in estimating the time taken to change babies wholly on to yolac or hemolac. The amount of breast milk was usually small, and the average gain in weight of these babies was not better than that of the whole groups.

WEIGHT. The yolac babies gained on the average rather more slowly than the controls : yolac babies 3·98 ounces and hemolac 4·30 ounces weekly ; the difference per month, however, only amounted to $1\frac{1}{3}$ ounces (see table 4). If the cases are sub-divided by season the control groups show a slightly superior gain both in winter and in summer. Again, if a weight curve is plotted from the average weight at each monthly birthday (see chart I and table 5), the controls are superior in weight from five months to eighteen months, and thereafter the number of babies is small. At six months this difference is about

13 ounces, at nine months about 9½ ounces, at twelve months about 2 ounces, and at eighteen months about 7 ounces. Taking the figures from this chart, we find (see table 6) that, between five and eighteen months old, the average monthly gain in the two groups differs by less than 1 ounce. But from two to five months old the controls gain rather better, i.e. 1 pound 10½ ounces monthly as against 1 pound 8½ ounces in the yolac group. Whether the difference in the rate of gain is statistically significant or not was not determined. Owing to the different length of attendance the process of determining this would be laborious, and in any case the difference is small.

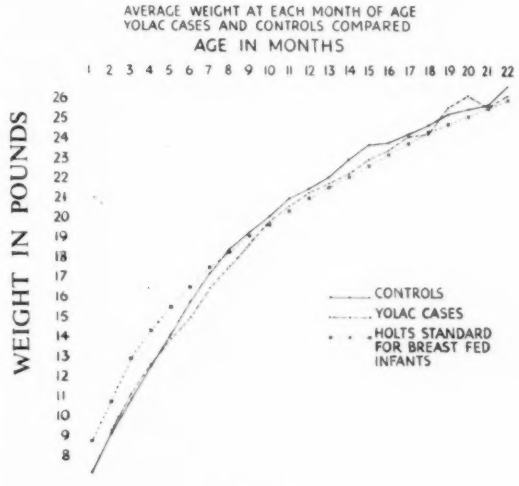
AVERAGE WEIGHT AT EACH MONTH OF AGE
YOLAC CASES AND CONTROLS COMPARED
AGE IN MONTHS
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
WEIGHT IN POUNDS
26 25 24 23 22 21 20 19 18 17 16 15 14 13 12 11 10 9 8
CONTROLS
YOLAC CASES
HOLTS STANDARD FOR BREAST FED INFANTS

CHART I

TABLE 4

THE AGES AND WEIGHTS OF THE YOLAC CASES AND CONTROLS COMPARED

WHOLE PERIOD	NO. OF CASES	SEX		AVERAGE AGE		AVERAGE ATTEND-ANCE,	AVERAGE WEIGHT		AVERAGE TOTAL GAIN,	AVERAGE WEEKLY GAIN,
		M.	F.	FIRST ATTEND-ANCE, MTH. DAY	LAST ATTEND-ANCE, MTH. DAY	MTH. DAY	FIRST ATTEND-ANCE, LB. OZ.	LAST ATTEND-ANCE, LB. OZ.	LB. OZ.	OZ.
Yolac cases	48	27	21	2 7·9	11 20·5	9 12·6	9 2·8	19 3·3	10 0·5	3·98
Controls	102	63	39	2 8·1	11 1·7	8 23·6	9 1·6	19 3·4	10 3·4	4·30
SUBDIVIDED BY SEASON	NO. OF PERIODS *									
SUMMER—										
Yolac cases	50			6 6·6	9 9·7	3 3·1	14 3·2	17 10·8	3 7·6	4·18
Controls	92			5 27·9	9 16·5	3 18·6	14 1·2	18 4·6	4 3·4	4·34
WINTER—										
Yolac cases	64			6 1·7	10 19·9	4 18·2	13 12·3	18 8·3	4 12·0	3·85
Controls	143			6 3·6	10 2·5	3 28·9	13 14·8	18 7·4	4 7·4	4·27

* In the seasonal subdivisions children attending during more than one summer or winter period cause the number of ' periods ' of attendance to be in excess of the number of children attending.

TABLE 5

AVERAGE WEIGHT AT EACH MONTH OF AGE—FIGURES ON WHICH CHART I IS BASED

AGE IN MONTHS	1	2	3	4	5	6	7	8	9	10	11
	lb. oz.	lb. oz.	lb. oz.	lb. oz.	lb. oz.	lb. oz.	lb. oz.	lb. oz.	lb. oz.	lb. oz.	lb. oz.
Yolac cases :											
Average weight ..		9 5·5	11 2·6	12 9·2	13 15·2	14 15·9	16 7·2	17 8·8	18 10·4	19 13·7	20 9·6
No. of cases	—	16	34	44	42	42	38	31	28	25	22
Controls :											
Average weight ..	7 1·4	9 2·6	10 13·0	12 8·4	14 2·0	15 12·8	17 3·7	18 16·6	19 4·0	20 1·0	20 15·3
No. of cases	7	34	69	87	86	75	66	62	54	50	45

AGE IN MONTHS	12	13	14	15	16	17	18	19	20	21	22
	lb. oz.	lb. oz.	lb. oz.	lb. oz.	lb. oz.	lb. oz.	lb. oz.	lb. oz.	lb. oz.	lb. oz.	lb. oz.
Yolac cases :											
Average weight ..	21 5·2	21 12·3	22 3·7	22 15·2	23 6·6	24 2·8	24 4·1	25 8·4	26 3·1	25 10·8	26 1·8
No. of cases	17	14	14	13	12	12	10	7	7	6	6
Controls :											
Average weight ..	21 7·1	22 0·7	22 14·9	23 11·4	23 13·6	24 4·4	24 11·0	25 3·7	25 7·5	25 11·1	26 10·0
No. of cases	40	34	27	24	20	20	16	13	11	11	8

TABLE 6

RATE OF GAIN IN WEIGHT AT DIFFERENT AGES (TAKEN FROM CHART I) YOLAC CASES AND CONTROLS COMPARED

AGE PERIOD	MONTHLY GAIN	
	YOLAC CASES	CONTROLS
2–5 months	1 lb. 8·6 oz.	1 lb. 10·5 oz.
5–12 months	1 lb. 0·8 oz.	1 lb. 0·7 oz.
12–18 months	0 lb. 7·8 oz.	0 lb. 8·7 oz.

HAEMOGLOBIN LEVEL. The haemoglobin level was examined monthly for babies in the yolac group and babies in group 2 (i.e. those ordered hemolac and cod-liver oil) (see chart II and table 7). The blood was taken from the heel from a prick with a cutting needle, and was estimated with a Haldane haemoglobinometer (Price Jones standard) (Mackay, 1933). This control group had at each month from five to eighteen months old an average haemoglobin level of over 80 per cent., excepting at fourteen months old, when the figure was 79·5 per cent. ; the average of all the estimations (304) done on

babies between the ages of five and eighteen months was 82·1 per cent. This average has been somewhat lowered by a few babies who were said to be having hemolac bought from a welfare centre, but who were pretty certainly not getting their medicated milk regularly. Two babies in this series had at some time after four months old a haemoglobin level under 70 per cent., presumably from this cause.

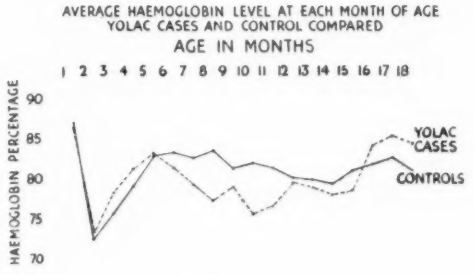

CHART II

TABLE 7

HAEMOGLOBIN LEVEL AT EACH MONTH OF AGE—FIGURES ON WHICH CHART II IS BASED

AGE IN MONTHS	1–2	2–3	3–4	4–5	5–6	6–7	7–8	8–9	9–10
Yolac cases—									
Haemoglobin percentage	86·7	73·5	78·4	81·4	83·4	81·5	79·4	77·4	79·0
No. of cases	14	30	40	43	37	39	34	29	23
Controls (Group 2 only examined)—									
Haemoglobin percentage	87·0	72·5	75·9	79·2	82·8	83·4	82·7	83·7	81·3
No. of cases	9	28	37	40	39	38	34	30	25

AGE IN MONTHS	10–11	11–12	12–13	13–14	14–15	15–16	16–17	17–18	18–19
Yolac cases—									
Haemoglobin percentage	75·3	76·7	79·6	79·0	78·2	78·7	84·4	85·6	84·6
No. of cases	20	19	12	11	10	11	9	5	8
Controls (Group 2 only examined)—									
Haemoglobin percentage	82·0	81·7	80·2	80·0	79·5	81·2	82·0	82·9	81·2
No. of cases	20	22	19	18	15	13	12	10	9

The majority in the yolac group showed a satisfactory haemoglobin level, but there were some exceptions. Four babies between the ages of eight and twelve months had a percentage between 46 and 60. The baby who dropped to 46 per cent. was a small twin suffering from diarrhoea, and was consequently off yolac at the time his haemoglobin reached this level, though it had been dropping previously on yolac. The other three babies were getting yolac

regularly. These four babies were given ferrous sulphate, and responded to it, showing that they had suffered from a deficiency of iron. Five other babies had at some time after five months old a haemoglobin level below 70 per cent., making nine in all below 70 per cent., as against two included in the 'iron' group, both of whom probably failed to get their iron ration. The majority in the yolac group had a haemoglobin level well above that to be expected in babies given dried milk with no added iron (Mackay, 1933). In chart II and table 7 are shown the average haemoglobin levels of yolac babies. (It must be noted that the figures for the four cases given iron were omitted from the comparison from the date of starting iron, so that the averages after eight months are thereby slightly raised.) The yolac babies drop from 83 per cent. at five months old to 75 per cent. at ten months old, and thereafter gradually rise to over 80 per cent. The average of all the 267 estimations done between five and eighteen months old on yolac babies not receiving iron was 79·9 per cent., i.e. only about 2 per cent. below the hemolac cases.

Hence replacing 50 per cent. of the milk in the diet with soya bean flour much diminished, but did not entirely prevent, the development of nutritional anaemia. The actual degree of improvement effected by giving yolac cannot be stated, as there was not a simultaneous control series on dried milk without added iron, but, in the author's previous work, a bottle-fed series of infants not getting added iron fell steadily from nearly 76 per cent. haemoglobin at five months old to 69 per cent. by twelve months old (Mackay, 1933).

CALCIFICATION OF BONES. Seventy-six radiographic examinations were made in the late winter or spring months on twenty-six children in the yolac group and thirty children in the control group, aged four months and upwards. In each case the films showed the whole of the forearm bones, the whole of the leg bones and the lower end of the femur. Three children were thought by the author to show some evidence of mild rickets which had already healed, but had left some cupping or irregular calcification at the lower end of the ulna : two of these were control cases and one was a yolac case. The changes were extremely slight in each case (in fact, two of the three considered as rachitic by the author were passed as normal by the radiologist), and, so far as could be ascertained, the babies had had their vitamin emulsion fairly regularly. As in every series of films of babies' bones, minor deviations from the normal were found, i.e. there was sometimes some osteoporosis present and sometimes slight lipping at the lower end of the ulna, but these cases were no more numerous in the yolac group than among the controls. Hence yolac with cod-liver oil proved as satisfactory as dried milk with cod-liver oil from the standpoint of bone calcification.

MORBIDITY RATES. (a) GENERAL. In order to compare morbidity rates, illnesses were counted from the babies' weight charts as described in previous papers (Mackay and Goodfellow, 1931). Every infection accompanied by a loss of weight or retardation of gain in weight was counted as an illness. Sometimes such a loss in weight would be missed because weight was regained before the next attendance, but this applies to both groups alike. Every infectious fever and every case of otorrhoea was also counted an illness. The general

morbidity rates are shown in table 8. The total morbidity rate is almost the same in the two groups, but the incidence of infections of the respiratory tract and of the gastro-intestinal tract differs. The yolac cases show an excess over the controls of gastro-intestinal upsets, and controls an excess of respiratory tract infections. Closer examination shows that the chief difference in the group of respiratory infections is that there are fewer cases of bronchitis recorded in the yolac group. A possible explanation is that when suffering from any infection, babies fed on yolac show a greater tendency to loose stools than do those fed on hemolac, and that this may have resulted in some cases of primary bronchitis in the yolac group being classified as enteritis. The total morbidity rate among yolac cases and controls was similar.

TABLE 8

GENERAL MORBIDITY RATE—YOLAC CASES AND CONTROLS COMPARED

	YOLAC CASES		CONTROLS	
No. of infants	48		102	
Average attendance	9 months 12·6 days		8 months 23·6 days	
No. of child-months	$452\frac{1}{10}$		$896\frac{7}{15}$	
DISEASE	NO. OF ATTACKS	NO. PER 100 CHILD-MONTHS	NO. OF ATTACKS	NO. PER 100 CHILD-MONTHS
RESPIRATORY TRACT—				
Cold in head and sore throat	50	11·1	110	12·3
Bronchitis	14	3·1	63	7·0
Pneumonia	1	0·2	1	0·1
Otorrhoea	11	2·5	11	1·2
		16·8		20·6
GASTRO-INTESTINAL—				
Diarrhoea and vomiting, or either	34	7·5	43	4·8
OTHER DISEASES—				
Specific fevers	7	1·6	13	1·4
Not otherwise classified	3	0·7	4	0·4
		2·2		1·9
Total	120	26·5	245	27·3

(b) LESIONS AFFECTING SKIN, MOUTH AND EYES. The incidence of lesions of the mouth and eyes (see table 9) is of a similar order in both groups, and in each case the total numbers are small. The total incidence of skin lesions is also similar but there are more infective skin lesions in the yolac group. Among infective skin lesions are classified all napkin area lesions with excoriations or pustules. Table 10 sets forth the incidence of lesions of the napkin area in the two groups of babies. The excess of infective skin lesions in the yolac group is the result of a greater frequency of excoriations and infections of the napkin area in this group, corresponding to the different character of the stools in the two groups.

STOOLS. The stools of the babies in the control groups fed on hemolac tended to be constipated, as is usual with babies fed chiefly on cow's milk. Even in young babies the stools were generally formed, though usually soft ; hard stools, however, were not uncommon. The presence of added iron in

the diet does not increase constipation. The colour was usually dark from the presence of iron—shades of greyish or blackish brown, perhaps with a tinge of green or yellow. The reaction to litmus, when tested (the stool brought to hospital might be one from the previous day), was nearly always alkaline whilst the babies were bottle-fed, but after mixed feeding was started, though alkaline or neutral stools predominated, slightly acid stools were fairly common. The odour was considered in excess of normal, and was offensive to a greater or lesser degree in, perhaps, one case in three. This tendency to offensive stools has been noted before with babies given iron (Mackay and Goodfellow, 1931), and both acid and alkaline stools might be offensive.

TABLE 9
LESIONS OF SKIN, MOUTH AND EYES—YOLAC CASES AND CONTROLS COMPARED

	YOLAC CASES		CONTROLS	
No. of infants	48		102	
Average attendance	9 months 12·6 days		8 months 23·6 days	
No. of child-months	$452\frac{1}{10}$		$896\frac{7}{15}$	
LESION	NO. OF ATTACKS	NO. PER 100 CHILD-MONTHS	NO. OF ATTACKS	NO. PER 100 CHILD-MONTHS
SKIN—				
'Infective' Excoriation, pustules, boils, intertrigo, external otitis.	103	22·8 } 61·1	149	16·6 } 59·0
'Non-infective' Erythema, peeling, chapping, papules, sudaminal rashes, urticaria.	173	38·3	380	42·4
MOUTH—				
Thrush or other stomatitis, ulcer or cracked lip	11	2·4	15	1·7
EYES—				
Conjunctivitis, blepharitis, and styes	7	1·5	15	1·7
Total	294	65·0	559	62·4

TABLE 10
LESIONS OF SKIN OF NAPKIN AREA—YOLAC CASES AND CONTROLS COMPARED

LESION	YOLAC CASES		CONTROLS	
	NO. OF ATTACKS	NO. PER 100 CHILD-MONTHS	NO. OF ATTACKS	NO. PER 100 CHILD-MONTHS
Excoriation, excoriated papules, pustules, boils	72	15·9 } 29·4	95	10·6 } 22·8
Erythema, peeling, chapping, papules	61	13·5	109	12·2

The stools of babies given yolac were usually softer, often not formed even in babies over a year old, though formed stools were common. In colour they were generally brown, often tinged with yellow, sometimes tinged with grey or green. The stools were homogeneous. Among those tested, the reaction to litmus was more often acid than in the control group, but an alkaline reaction preponderated. The odour was seldom offensive.

The number of stools passed daily was usually greater among the children fed on yolac. Sometimes a young baby who was doing well might have four or more stools in the day, which was uncommon in the hemolac group. Most commonly in children of both groups there were one or two stools daily, but the number with one stool in the day was distinctly smaller in the yolac group than in the control group, and yolac babies were less troubled with constipation.

URINE. The urine in the control groups was acid in the great majority of specimens tested. In the yolac group an alkaline urine was much more frequent, though after mixed feeding was started it was generally acid. This is in contrast with the alkaline urine of babies fed only on soya flour with added carbohydrate and fat, as described by Mader (1932).

TOLERATION OF FOOD. A large proportion of the babies were first brought to hospital on account of feeding difficulties. The mothers' statements as to excessive crying, fretfulness, vomiting and looseness of stools were recorded. Among the babies included in the comparison, complaints of crying and fretfulness during the first eight weeks of attendance were about equally common in the yolac and control groups, though complaints of loose stools and vomiting were more common in the yolac group. After starting yolac the number of stools often increased, and even in the absence of looseness, mothers might refer to the condition as diarrhoea. If looseness was not present, no change in the food was usually advised. In only one case did the author decide that a baby ought not to be kept on yolac : this baby had frequent small stools, some vomiting and some fullness of the abdomen on yolac, and apparently suffered from colic. After gaining only about 3½ ounces weekly for some weeks on yolac, he was changed by the author's advice on to unmedicated dried milk, with an immediate improvement, i.e. a good gain in weight and cessation of symptoms.

The reasons for stopping attendance may throw some light on the question of toleration. Of the children in the two groups, seventeen in the yolac group and thirty-six in the controls were discharged by the author on account of age or the termination of the investigation ; of the rest, thirty-one yolac cases (64·6 per cent.) and six[illegible]x controls (64·7 per cent.) ceased to attend without being discharged : i.e. the same proportion in each group. In some cases the mother said that she wished to change the food, that the child refused the yolac or hemolac, or that she was not satisfied with the baby's progress. This happened seven times with yolac babies (14·6 per cent.), and eight times with controls (7·8 per cent.). Certainly children of, say, twelve months old and upwards seem to tire more readily of yolac or hemolac than they do of unmedicated dried milk, and it is desirable to vary the taste by giving the food in different combinations.

To summarize, the impression was gained that yolac was less easily tolerated than hemolac ; but that begun gradually (as was always advised, but not always carried out by the mothers in the present investigation), the great majority of babies given yolac tolerated it well and had no colic or discomfort. It should not be given to a baby with a gastro-intestinal upset. A sudden change, contrary to advice, on to either yolac or hemolac certainly caused diarrhoea in some cases. When looseness did develop on either yolac or hemolac, the mother was asked temporarily to stop the feeds and give water only, gradually working back first on to a full feed of unmedicated dried milk and then gradually changing back to yolac or hemolac.

Babies excluded from the final comparisons. The number of cases taken on and the number finally excluded in each group were as follows :

YOLAC GROUP : taken on 80, finally excluded 32 (40 per cent.).
HEMOLAC PLUS COD-LIVER OIL GROUP : taken on 70, finally excluded 21 (30 per cent.).
HEMOLAC PLUS VITAMIN D GROUP : taken on 75, finally excluded 22 (29 per cent.).

In any investigation of this type the wastage of cases which cannot be used in the final comparison is bound to be large, but since the wastage in the yolac group was 40 per cent. and in the controls approximately 30 per cent., it is necessary to consider whether more dropped out of the yolac group because the food was less satisfactory. The analysis of the excluded cases (table 11) shows that whereas a rather smaller proportion dropped out of the yolac group than out of the other groups for reasons believed to be unconnected with the nature of the feeding advised, the number who dropped out because the baby was upset or was thought by the mother to be upset by the food was greater in the yolac group, which certainly suggests that the yolac was less easily tolerated. The hemolac was supplied to mothers at the price of 1*s.* 6*d.* per pound, the yolac at 1*s.* per pound. What psychological effect this had it is difficult to say ; but in some cases mothers whose babies cried probably suspected the ' cheap ' and unknown food yolac without sufficient justification. For example, three babies in the yolac group who were gaining well were changed by the mothers on to other foods ' because the baby was crying,' but, according to their subsequent statements, the babies continued to cry after the change. Probably if their babies had received hemolac, a name which many mothers would know, they would not so readily have interpreted the symptoms as indicating the need for a change in the food.

Discussion and conclusions

This investigation has demonstrated that babies can be reared, kept in good health, and grow well on the diet described, in which a soya flour (soyolk) has been used to replace half the milk in artificially fed babies' diets. The control cases, who received hemolac with vitamin additions and sugar, and later on, like the yolac cases, table food in addition, were getting as good a diet as

TABLE 11

CASES EXCLUDED FROM FINAL COMPARISON

	YOLAC		HEMOLAC AND COD-LIVER OIL		HEMOLAC AND VITAMIN D	
	NO.	PER CENT.	NO.	PER CENT.	NO.	PER CENT.
NO. OF CASES TAKEN ON.. ..	80	—	70	—	75	—
NO. OF CASES FINALLY EXCLUDED	32	40	21	30	22	29
For reasons unconnected with toleration of food—						
For pathological conditions which rendered case unsuitable	2		0		3	
For insufficient or wrong emulsion, or re-establishment of breast feeding	1	3	4	4	2	5
For reasons probably unconnected with nature of food—						
Treatment under one month—		10		11		12
1. Infants gaining at rate of 5 oz. and more weekly—		12·5		15·7		16·0
No complaints when last seen	3		1		4	
Intercurrent illness when last seen	—	7	2	7	—	7
2. Infants gaining less than 5 oz. weekly—						
Cause probably an infection or feeding disturbance present when first seen ..	4*		4*		3	
For reasons possibly connected with nature of food—						
Treatment under one month—						
1. Infants gaining at rate of 5 oz. or more weekly—complaints of crying, vomiting or diarrhoea	6†		4		1	
2. Infants gaining at less than 5 oz. weekly—no cause found apart from feeding difficulties	9	15	1	5	2	3
		18·8		7·1		4·0
Did not re-attend after ordered yolac or hemolac—reason unknown	7	8·8	5	7·1	7	9·3

* 1 died. † 3 babies were said to cry as much after change of food

the author could devise. The rate of gain in weight of the group of babies getting the mixture (yolac) of soya flour and dried milk was slightly inferior to that of the hemolac group, but perhaps rather better than would be obtained with unmedicated dried milk. The subnormal growth on unmedicated cow's milk is presumably the result of infections associated with iron deficiency. In every country where the subject has been investigated, anaemia in babies

and young children has been found to be common, and everywhere anaemia will predispose to infection and so diminish the rate of gain in weight. The use of yolac produced a fairly satisfactory haemoglobin level in most babies and a morbidity rate as low as produced by the use of hemolac, and hemolac halved the morbidity rate occurring with unmedicated dried milk by abolishing iron deficiency anaemia. The average period during which the babies received yolac without any other source of milk, and without any solid food, was about three-and-a-quarter months, from say two-and-three-quarter months to six months old. It is possible that with more prolonged bottle-feeding on yolac the results might have been less satisfactory. On the other hand, the babies who came under observation early and were on yolac from less than two months old, averaged at six months old 15 pounds 11·6 ounces, that is about $11\frac{3}{4}$ ounces more in body weight than the whole yolac group, so that their record is good. Since various authors have compared the weight curves of babies getting soya flour with Holt's standard, it may be of interest to note that both groups started considerably under Holt's standard (as one would expect, since they were subnormal children brought to hospital for advice), the controls passed above the standard at eight months old, the yolac cases at ten months old, and both remained above it till eighteen months old, after which the numbers are small.

Bone formation, as shown radiographically, is as good on the yolac diet as on dried milk (both groups receiving a vitamin D supplement), hence presumably the calcium-phosphorus ratio is satisfactory. Hard stools, which are so common with most artificially-fed babies, are not common with babies on yolac. The fact that yolac is not quite as easily tolerated as dried milk alone is a definite disadvantage. The author's impression is that yolac did give rise to colic or discomfort in some babies, but that if the change over to yolac was made sufficiently gradually most babies took it easily and without discomfort, and even those who experienced some discomfort at first usually became quickly accustomed to the food and any discomfort ceased. It is possible that boiling the yolac mixture would render it more easily tolerated and reduce the incidence of loose stools, but this could only be settled by another controlled investigation. Boiling was not advised in the present investigation for two reasons : the first was that if the preparation of the food given to one group of babies had been more troublesome and had cost more in fuel than preparing the food given to the controls, this would have introduced complicating factors, which might well have vitiated the comparison, as time and cost would militate against the regular administration of yolac. The second reason was that the simpler the method of preparation, the more likely it was that the mixture could be adopted in tropical countries, or for relief work among war refugees or others in circumstances where simplicity of preparation is important. The yolac and hemolac were both prepared by mixing the powder with water which had been brought to the boil. If the mixture had to be boiled after mixing this might tempt the mother to prepare twenty-four hours' supply at a time, which, in a poor home, is definitely contra-indicated on account of the certain contamination of the food by micro-organisms. It should be noted that in this investigation

if a baby developed diarrhoea neither hemolac nor yolac was given until the stools were normal, unmedicated dried milk being used instead. Moreover, when first seen, babies were habitually changed to unmedicated dried milk as a first step, and from this during another week gradually on to hemolac or yolac.

Wherever, as in London at the present time, dried milk, with or without iron, is obtainable for practically all babies, it is unlikely that yolac will be much used. But where this is not available, there seems every reason for trying to organize the supply of a preparation such as yolac—either imported or prepared from local produce. No doubt there would be many problems of packing and distribution to be solved in a hot climate, but if prepared on a large scale and distributed by some means eliminating retail costs it would seem that the price should be little more than half that possible for dried milk, for soya bean is cheap. Used in a hot climate by ignorant mothers the problem of diarrhoea may prove difficult, but nevertheless this mixture should be the means of saving many lives now lost through the want of any good substitute for breast milk. If the change to yolac has to be made suddenly, this could be done safely by starting the baby on a small amount, i.e. underfeeding at first and increasing gradually up to the baby's full needs. It was commonly said in London not many years ago that poor mothers would not learn to measure and mix dried milk, but events have proved this false. Since, the world over, women prepare and cook food, there seems no reason why the mothers of Africa or Asia should not learn to mix a milk-soya-bean powder with hot water.

In most tropical countries there should be no need to give vitamin D with yolac, and vitamin C could presumably be supplied without much difficulty from fresh fruit or vegetable juice. The vitamin A value of soya bean is said to be of the same order as that of average cow's milk (reckoned on dry weight), and there is no gross deficiency of vitamin A in average dairy milk, though its vitamin A value is much less than that of human milk (Dann, 1936 ; Meulemans and de Haas, 1938). The addition of vitamin A would increase the cost, so presumably where the element of cost is decisive any vitamin A addition would be omitted. The quantity of vitamin B complex, so far as evidence is available, should also be adequate.

Only one mixture of dried milk and soya bean has been tried out in this work. The obvious question arises whether, if this mixture cannot be produced at a low enough price to meet the economic circumstances of a country, any further modification could render it cheaper and still adequate, pending the time when cow's milk in some form will be available for all who may require it. It is possible that one of the following modifications might prove as satisfactory : soya flour with a half-cream dried milk, or even with skimmed milk, and a larger proportion of sugar than was used by the author, or a mixture containing more than 50 per cent. soya flour. With the findings here recorded, and those of Rittinger and his associates, which prove that the use of a soya-bean-cow's-milk mixture as an infant's food is justified by its results, it is hoped that others will try out this or other modifications where the problem of milk shortage is acute.

For older children and even adults the mixture should also prove useful, though here certain additional facts must be borne in mind. The inclusion of say three-quarters to one pint of milk, full-cream or even skimmed, improves the growth and well-being of schoolchildren of the working classes in this country (Leighton and Clark, 1929). This is proven, and is true for other countries also. It is generally agreed that the full-cream milk supplement is effective because it is fitted to meet any deficiency, except iron, in greater or less degree, and the deficiencies in one child's diet will not necessarily be the same as those of his next door neighbour, let alone those of another child in another continent. Soya bean, on the other hand, in spite of its valuable constituents, may not make good some of the deficiencies common in the area ; for example, Aykroyd and Krishnan (1937) found that a supplement of soya bean did not render the diets of school-children in Southern India satisfactory. Hence if asked whether, in such circumstances, a supplement of one pint of milk daily or of half a pint of milk with an equivalent number of calories in soya bean should be chosen, evidence favours the pint of milk, but the second, nevertheless, would probably prove a good second best. The insipid taste of yolac is definitely unattractive, but it has no objectionable taste and it can easily be used in combination with other foodstuffs, cooked or uncooked. If yolac is mixed in bulk for groups of children, the rapidity with which the soya flour begins to sink to the bottom would be a definite difficulty, but one which could probably be overcome, e.g. by cooking.

It is desirable to ascertain that the soya flour is prepared and packed under proper hygienic conditions, since it may otherwise contain many organisms, including spore-bearers.

Summary

This paper is concerned with the efficacy of a cheap substitute for breast milk, in the form of a soya flour with dried milk powder. The composition, nutritive value and uses of soya bean flours for infant feeding, as described chiefly by American and Chinese writers, are discussed.

The author's work is a comparison of the progress made by two groups of babies living in their own homes and attending the Queen's Hospital for Children in London. The first group received till six months old a mixture (yolac) of equal parts of full cream roller process dried milk and a soya bean flour, prepared by a modification of the Berczeller process, together with a supplement of cod-liver oil ; the controls received dried milk with added iron (hemolac), and a supplement of cod-liver oil or vitamin D emulsion. Both received orange juice. After six months old the babies were given a mixed diet, the first group continuing to have yolac, about one to one-and-a-quarter pounds weekly, the second the same amount of hemolac, providing them with about one pint of milk daily.

The observation lasted from July, 1935, to March, 1938, and 48 ' yolac babies ' and 102 controls are included in the final analysis. The average age at the first attendance was the same to a day, i.e. 2 months 8 days ; the average

weight differed by about 1 ounce, and was a little over 9 pounds. The average period of attendance was 9 months 13 days and 8 months 24 days respectively.

Both groups made good progress ; the average weekly gain in weight of the controls (4·3 oz.) was slightly superior to that of the yolac cases (3·98 oz.), the difference being about $1\frac{1}{3}$ ounces per month. The average weight curve of the controls was superior to that of the yolac cases from about six months onwards ; the difference in weight at six months is about 13 ounces, and at twelve months about 2 ounces. Since the difference was small the determination of whether or not it was statistically significant seemed of small practical importance, and as the period of attendance varied the determination would be laborious and was therefore omitted.

The babies in the yolac group for the most part showed a satisfactory haemoglobin level, but four babies dropped to 60 per cent. haemoglobin or less, and these were treated with iron. The average haemoglobin level from five to eighteen months old of the babies in the yolac group was about 80 per cent., or about 2 per cent. lower than the average of the hemolac group, but it was higher for the whole of this period than would be found in babies fed on unmedicated dried milk.

The total morbidity rate of the yolac group was about the same as that of the controls, and therefore better than would be expected with babies fed on milk without added iron. On the other hand the tendency to loose stools was greater in the yolac group. Calcification of the bones was as good in the yolac group as in the control group.

Yolac is not as easily tolerated as full cream dried milk, and should be started gradually : so started it is, with a few exceptions, well tolerated, though in some cases it appears to give rise to some abdominal discomfort at first. If it is impossible to make the change from the existing feed gradually, yolac should be given in very small quantities at first, taking about a week to get the baby on to its full calorie requirements.

A mixture of equal parts of dried milk and soya bean flour, such as used in this investigation, provides an infant food on which babies make good progress. It should be possible to market it at a price much lower than that of full-cream dried milk, and it is suggested that owing to its relative cheapness it merits extended trial in countries where, for economic reasons, a satisfactory substitute for breast milk has hitherto been unobtainable.

Thanks are due to all those who by their generous co-operation made this work possible : to Sister F. M. Westbrook and the nurses in the out-patient department for constant help at the clinics ; to Miss L. Goodfellow ; Miss L. E. Jacob, M.P.S., and the dispensary staff ; the almoner, Miss M. Wright ; and to Harry Loxton for his excellent technical assistance until the day of his death in a street accident. Mr. J. Tavroges, B.Sc., chemist to the Cow and Gate firm, supervised the preparation and supply of the yolac.

References

Adolph, W. H., and Shen, C. H. (1932). *J. Nutrit.*, **5,** 379.
—— and Kao, H. C. (1932). *Chin. J. Physiol.*, **6,** 257.
—— —— (1934). *J. Nutrit.*, **7,** 395.
Aykroyd, W. R., and Krishnan, B. G. (1937). *Indian J. med. Res.*, **24,** 1093.
Bailey, L. H., Capen, R. G., and Le Clerc, J. A. (1935). *Cereal Chem.*, **12,** 441.
Becker, C. (1934). *Arch. Verdauungskr.*, **56,** 260.
Blackfan, K. D., and Wolbach, S. B. (1933). *J. Pediat.*, **3,** 679.
Bruce Jones, D., and Waterman, H. C. (1921). *J. biol. Chem.*, **46,** 459.
Caldwell, G. W. (1933). *Med. J. Rec.*, **138,** 126.
Chang, K. J., and Tso, E. (1931). *Chin. J. Physiol.*, **5,** 199.
Dam, H. (1935). *Biochem. J.*, **29,** 1273.
Dann, W. J. (1936). *Ibid.*, **30,** 1644.
Ferrée, C. J., Translated by Ferrée, C. J., and Tussaud, J. T. (1929). *The Soya Bean and the New Soya Flour*, London, p. 14.
Guy, R. A., and Yeh, K. S. (1938a). *Chin. med. J.*, **54,** 1.
—— (1938b). *Loc. cit.*, 101.
Hayward, J. W., Steenbock, H., and Böhstedt, G. (1936a). *J. Nutrit.*, **12,** 275.
—— (1936b). *Ibid.*, **11,** 219.
Hill, L. W., and Stuart, H. C. (1929). *J. Amer. med. Ass.*, **93,** 985.
Horvath, A. A. (1938). *Amer. J. Digest. Dis.*, **5,** 177.
Klein, J. (1933). *Arch. Pediat.*, **50,** 205.
Leighton, G., and Clark, M. L. (1929). *Lancet*, **1,** 40.
Mackay, H. M. M., and Goodfellow, L. (1931). *Med. Res. Council, London, Spec. Rep. Series, No.* 157.
Mackay, H. M. M. (1933). *Arch. Dis. Childh.*, **8,** 221.
—— (1939). *Ibid.*, **14,** 245.
Mader, A. (1932). *Mschr. Kinderheilk.*, **54,** 212.
Meulemans, O., and de Haas, J. H. (1938). *Amer. J. Dis. Child.*, **56,** 14.
Miller, H. W., and Wen, C. J. (1936). *Chin. Med. J.*, **50,** 454.
Osborne, T. B., and Mendel, L. B. (1917). *J. biol. Chem.*, **32,** 369.
Reid, E. (1935a). *Chin. J. Physiol.*, **9,** 27.
—— (1935b). *Loc. cit.*, 307.
Rittinger, F. R., and Dembo, L. H. (1932). *Amer. J. Dis. Child.*, **44,** 1221.
——, ——, and Torrey, G. G. (1935). *J. Pediat.*, **6,** 517.
Ruhräh, J. (1909a). *Arch. Pediat.*, **6,** 496.
—— (1909b). *J. Amer. med. Ass.*, **54,** 1664.
—— (1915). *Amer. J. med. Sci.*, **150,** 502.
Schall, H., and Heisler, A. (1917). *Nahrungsmitteltabelle*, Wurzburg, 5th edition.
Sherman, H. C. (1937). *Chemistry of Food and Nutrition*, New York, 5th edition, 368.
Sinclair, J. I. (1916). *N.Y.St. J. Med.*, **16,** 83.
Stearns, G. (1933). *Amer. J. Dis. Child.*, **46,** 7.
Tso, E. (1928). *Chin. J. Physiol.*, **2,** 33.
—— (1929). *Ibid.*, **3,** 353.
——, and Chu, F. T. (1931). *Ibid.*, **5,** 287.
——, Yee, M., and Chen, T. (1928). *Ibid.*, **2,** 409.
Wan, S. (1932). *Ibid.*, **6,** 35.
Willstaedt, H., and With., T. K. (1938). *Z. physiol. Chem.*, **253,** 133.

THE SCHILLING HAEMOGRAM IN OTITIS MEDIA AND MASTOIDITIS OF INFANCY

BY

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In 1938 a survey of the incidence of otitis media and mastoiditis in infancy was published from Alder Hey Children's Hospital (McConkey and Couper, 1938). A clinical classification of such cases was suggested and conclusions were drawn regarding the relative merits of conservative and operative treatment. Simultaneously a second and more detailed investigation was in progress, with certain aspects of which this present communication is concerned.

This second series consists of fifty infants under the age of one year, suffering with an illness characterized by otitis media (sometimes with mastoiditis), and varying degrees of diarrhoea and vomiting. More than half of these children were judged to be suffering from the so-called latent mastoiditis, i.e. they all suffered from otitis media but there were no external signs of involvement of the mastoid process. Four cases, presenting the classical clinical picture of mastoiditis, were also included. The question of diagnosis and treatment is one of great difficulty and importance and briefly resolves itself into two major problems (a) to decide if infection has spread to the mastoid process, and (b) to decide if operation is advisable, and if so, the best time for this treatment.

In an endeavour to find some reliable indication of prognosis, of whether the mastoid antrum was involved or not, and of the optimum time for operation, a series of Schilling counts was performed on each case. There is a great mass of literature on the subject of these counts and their application to all sorts of conditions. For the present purpose it is sufficient to state that the Schilling count is a modification of Arneth's original method of classifying the polymorphonuclear cells into young and old. In the present work additions to the Schilling count elaborated by Crocker and Valentine in 1934 have also been employed.

Schilling in 1911 divided the polymorphonuclear cells into four groups, i.e. segmenters, stabs, juveniles and myelocytes, the segmented cells being regarded as old cells and the others as young forms. The division of the cells into these four groups gives a qualitative analysis of the neutrophilic cells available to combat the infection. The normal adult picture shows no myelocytes, no juveniles, four stabs and sixty-four segmenters, a total of sixty-eight

neutrophils in each one-hundred white cells ; an increase in the number of young forms, i.e. myelocytes, juveniles and stabs with a decrease in the number of segmenters constitutes the well-known ' left shift,' the degree of ' shift ' indicating the severity of the stimulation undergone by the bone marrow. Conversely an increase in the number of segmenters with a fall in the number of young forms indicates a return to normality. If the type of left shift consists only of stabs, it is termed degenerative ; if of stabs, juveniles and a few (four) myelocytes regenerative, if more than five myelocytes appear leukaemoid, and the type of left shift is a measure of the intensity of the intoxication. The Schilling Index is the ratio of combined shift cells to segmenters, i.e. in the normal adult 4 : 64 or 1/16 or ·06. The multiple index (Crocker and Valentine) is the Schilling index multiplied quite arbitrarily by sixteen, giving a normal of one, a simpler number to work with.

The total white count and the ordinary differential count afford information regarding the quantitative strength of the white cells, i.e. the total white count is an estimation of the total number of white cells available in the circulation, and the ordinary differential count gives the percentage of neutrophils in the total white count. In other words these two counts indicate the reproductive power of the bone marrow for producing neutrophilic cells to combat the infection. On the other hand the Schilling count is an estimation of the qualitative strength of the cells in the circulation, i.e. the marrow ' threshold,' a mechanism whereby the maturity of the cells passing into the blood stream is controlled. The marrow threshold is depressed when a large number of immature cells are allowed to escape into the blood stream, producing a shift to the left.

The actual method employed in performing the counts was as follows :—

Heel blood was invariably used because a more satisfactory flow of blood without having to resort to rubbing or pressure may be obtained from this area, and the cases under investigation were cases of otitis media, frequently with discharge, rendering the use of the lobe of the ear inadvisable. The blood was taken off in glass pipettes and immediately conveyed to glass tubes containing the requisite amounts of diluting fluids. Total red counts were not made except in a few cases. The films were spread on ordinary microscopic slides employing a spreader. The spreader consisted of a microscopic slide, two adjacent corners of which had been cut off, giving an edge somewhat narrower than the width of an ordinary slide. Films thus prepared were narrower than the slide bearing them, and the two edges were available for inspection. One series of films was stained with Leishman's stain and another with Wright's stain, but the same stain was employed throughout any one case. The average of two total white counts, made with a Türck ruling, was taken at each estimation. Two hundred cells were counted in each differential count and percentages calculated therefrom, and the neutrophilic cells were then ' Schillingized ' by counting an additional two hundred neutrophils. The Schilling index, or ratio of shift cells to segmenters was calculated from the figures so obtained and the multiple index obtained by multiplying the Schilling index by sixteen.. Thus in each film the differential count and the Schilling count involved the counting of four hundred cells.

The foregoing remarks apply to the adult blood picture and some consideration of the differences encountered in the infantile blood picture is necessary. According to Schilling there are haematologically three groups: the new-born infant, the nursling and the child from one to six years. The blood picture in the nursling, from which group all the present cases are drawn, remains constant in the first year and up to the middle of the second,

after which it changes gradually towards the adult picture, attained about the sixth year. The total white count in the nursling group is somewhat higher than in the adult.

The following are figures quoted by Schilling :—

Gundobin	9000—15,000
Benjamin	8000—12,000
Romiger	9200—23,700
Hoffman and Welker	6200—21,600

Washburn (1934 and 1935) found that the total white count varied from 5000 to 24,000, the majority being between 8,000 and 16,500. A high proportion of lymphocytes is characteristic and certain authors describe a slight left shift. Others, notably Ockel (1924) and Schüssler (1924), deny the existence of this slight shift in the normal infant. Ockel stated that ' a left shift in the Arneth sense is not observed in completely normal infants or in the application of the Schilling method,' and Schüssler said ' only exceptionally have I encountered an increase of stab-nuclear forms over 4–6 per cent. without its being possible to find an explanation for it from the condition of the child.' He concluded that the degree of shift is quite independent of age. These authors give their figures and it has been possible to work out the Schilling index as it has been done in the present work. Figures so obtained have been added to the following table of comparative figures, which is quoted from Schilling :—

AUTHOR	BAS.	EOS.	MYEL.	JUV.	STABS.	SEG.	LYMPH.	MON.	SCH. I.
Ockel	0·5–1	1–5	—	0–1	0–5	15–40	49–75	3–12	·05
Hoffman and Welker.. ..	0–1	0–7	—	0–2	0–9·5	5–49	42·5–90·5	0–16	·23
Schüssler ..	—	2	—	—	2	29	61	6	·06
Romiger	0–1	2–4	—	0–5	8	16	62–69	6	1·2
Adult Schilling	0–1	2–4	—	0–1	3–5	51–67	21–35	4–8	·08

Schilling haemogram in normal infants

In view of these conflicting figures a series of twenty normal infants was investigated. These infants were admitted for the operation of circumcision, inguinal hernia, and the like, and were carefully examined for the presence of infection. The average of the figures obtained is as follows :—

HAEMOGLOBIN, PER CENT.	64
TOTAL WHITE COUNT	11,990
MULTIPLE INDEX	1·1
SCHILLING INDEX	0·07
STABS	7
SEGMENTERS	93
TOTAL NEUTROPHILS	3094
PERCENTAGE POLYMORPHONUCLEARS ..	26
,, MONOCYTES	10
,, LYMPHOCYTES	58
TOTAL LYMPHOCYTES	6902
PERCENTAGE EOSINOPHILS	4
,, MAST CELLS	0·5

The average total white count and differential count coincide with findings elsewhere, and the results of the Schilling count were found to agree with those who deny a normal left shift, the average Schilling index being 0·07. No juveniles or myelocytes were found. The multiple index throughout has been obtained by multiplying the Schilling index by sixteen. The arbitrary figure sixteen has been used but it will be obvious that it is of no consequence what figure is used provided the same figure is used throughout the series. The only advantage of the multiple index is that it gives more convenient numbers to work with.

Except in the case of the first count, which was taken at whatever hour of the day the child happened to be admitted, the blood for this series was taken between 10 a.m. and 11 a.m., i.e. shortly after the 10 a.m. feed. In view of this it was considered advisable to investigate what effect, if any, feeding had upon the various estimations. A series of counts was therefore taken before and after feeds. The blood was taken half-an-hour before each feed and one hour after the start of each feed, the feed lasting from fifteen to twenty minutes. As each infant was fed at 10 a.m., 2 p.m. and 6 p.m. six counts were obtained throughout the day. Four normal infants were so investigated.

The following is an abbreviated result of one of those investigations, the others being similar.

FEED	TIME	TOTAL WHITE COUNT	MULTIPLE INDEX
10 a.m.	Before	13,900	·96
	After	10,300	·64
2 p.m.	Before	9400	·80
	After	10,600	1·1
6 p.m.	Before	12,700	1·1
	After	9500	1·2

It will be seen that feeding appears to exert no systematic effect on these estimations. In 1900 Japha conducted experiments on fourteen healthy infants, i.e. infants who had recovered from a variety of illnesses, and came to the conclusion that ' in the infant digestive leucocytosis cannot be regarded as a phenomenon occurring with any regularity.' A similar finding was recorded among sick children. Mitchell in 1915 came to the conclusion that bottle-fed babies do not constantly show digestive leucocytosis. Sabin et al. (1925) made no mention of infants. In 1927 Fletcher and Mitchell said that there are marked daily variations but ' any variation in the leucocyte count, which can be interpreted as a digestive leucocytosis, is inconstant.' Washburn (1934), stated that ' there is no demonstrable correlation between the variations in the number of white cells and such factors as intake of food, digestion, sleep, increased activity or minor external disturbance.'

Rogatz (1930) commented favourably on the use of the Schilling count in a series of cases, the majority of which were under one year. In 1934 Klenerman found much higher proportions of ' band ' forms in infantile bloods and went so far as to state that very few polymorphs show true segmentation. Martin and Ellenberg (1935) confirmed the usefulness of the Schilling count in children, but Washburn (1935) thought the method too time-consuming.

Schilling haemogram in aural infection

There is little to be found in the literature regarding the effects of aural infection on the blood picture especially in infancy, and a large proportion of the work done deals with older children and adults.

The earliest available work applying haematology to otology was by Darling (1908). He concluded, from work done on patients of all ages, that 'the number of leucocytes per c.mm. was an indication of the body reaction to infection,' and he found that repeated examination was of greater value than a single estimation. Also in 1908 Dench came to the conclusion that the differential count was of no value as an aid to diagnosis. Gale in 1928 found left shift and an index calculated therefrom unreliable in making a diagnosis in otological complication, e.g. perisinus abscess, and of no help in determining when to operate. In 1931 Rosenwasser and Rosenthal found total white counts and ordinary differential counts inadequate and the Schilling count of great value as a diagnostic aid in otitic infections. Applied to ear infections Weiss (1931) found that 'staff' counts were useless as a diagnostic aid or as an indication for operation, because cases of acute otitis media often showed higher 'staff' counts than cases of mastoiditis, but when used in a series they are of 'inestimable importance in prognosis.' Boies (1931) reported similar findings. Alden and Demotte (1931) who are in agreement regarding the usefulness of the 'staff' count, stated that it 'offers a much more reliable index of the patient's condition than does the polymorphonuclear percentage of the total white count and particularly in children, than the pulse and temperature variations.' No work has been found on the application of these counts to otitis media and the so-called latent mastoiditis of infancy.

It would be impossible in the space available to describe fully the fifty cases examined by this method. Therefore seven illustrative cases have been selected and the following is a detailed description of these cases. Each case consists of (1) a short clinical summary giving dates of admission, discharge, age, sex, result, history, condition on examination, progress while in hospital and results of investigations and post-mortem examination, if any, and (2) a graph with description, plotting the infant's weight, total white count, total polymorphonuclear count and multiple index, and showing dates upon which myringotomies or posterior drainage were performed. At the bottom of each graph a simple line indicates the dates during which the infant's ear or ears were discharging and below this line a block graph indicates the number of stools passed per diem.

Case reports

Case 1.

M. M., female, aged 9½ months, was admitted on 26.9.36 and discharged on 4.1.37.

HISTORY. There was a history of two loose, green stools on the evening before admission. The infant had been taking its feeds well.

CONDITION ON EXAMINATION was fair with no dehydration. The right tympanic membrane was injected and bulging, but other examination negative. Temperature was 99° F.

PROGRESS. Right myringotomy was performed but no pus obtained. Condition improved until 12.10.36 when temperature rose to 99° F., and weight-

loss began. Both tympanic membranes were very injected, the right bulging slightly posteriorly. On 14.10.36 left tympanic membrane was bulging, left myringotomy was performed, and pus released. On 17.10.36 further weight-loss occurred and the right tympanic membrane was still very red and bulging somewhat. Right myringotomy was performed but no pus obtained. On 21.10.36 the infant lost 14 oz. in weight. Bilateral posterior drainage was performed ; on the left side the bone was hyperaemic while there was pus on the right side with rather soft bone. On 29.10.36 both wounds were satis-

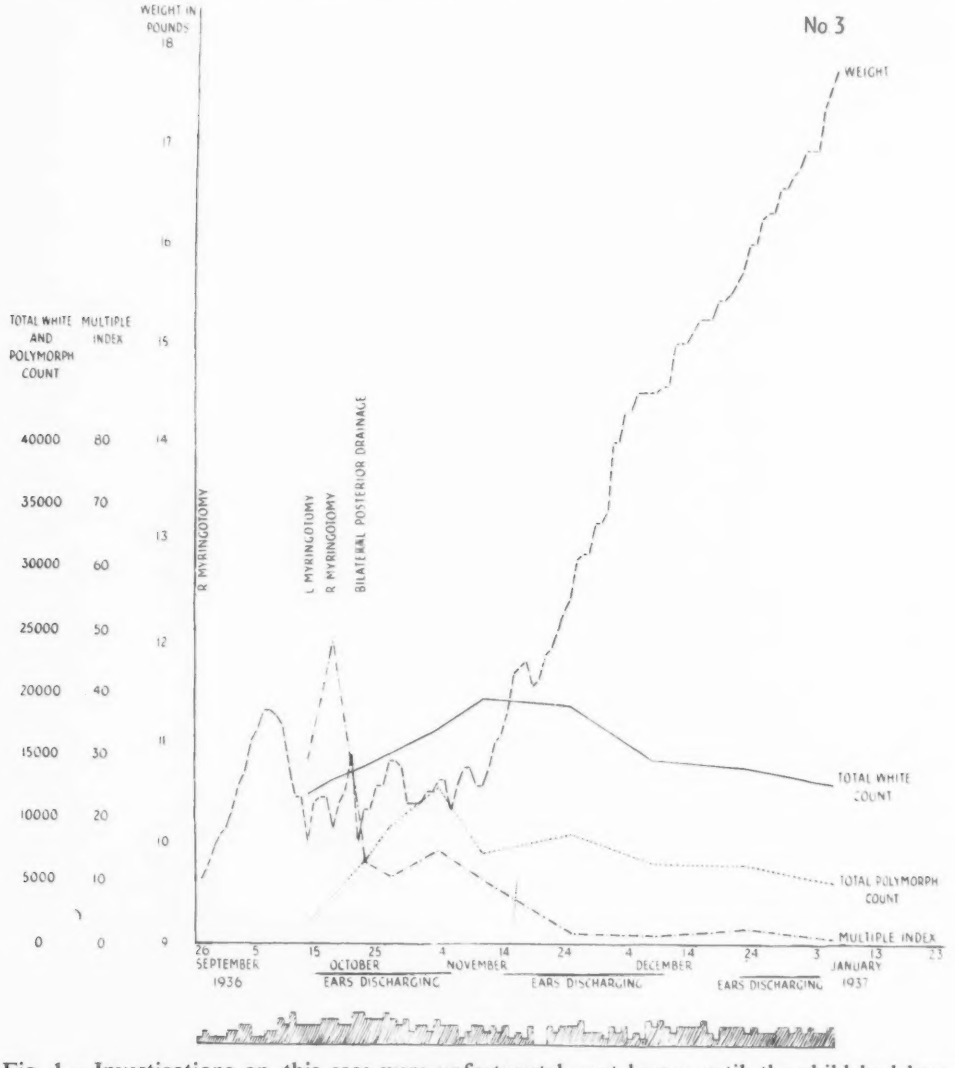

Fig. 1.—Investigations on this case were unfortunately not begun until the child had been in hospital for some time. The multiple index was high at first estimation and rose sharply. It then fell considerably and was actually falling at time of operation. Decision to operate was made on account of the heavy weight loss which occurred on 21.10.36 and the child's poor general condition ; it was becoming toxic. The fact that multiple index was falling at time of operation and, although it remained elevated, it was a lower figure, suggests that possibly the infant might have recovered without operation. It will be noticed that the beginning of the fall of multiple index to normal coincides with the start of the infant's final gain in weight, i.e. the two curves diverge. The total white count was never markedly elevated and was rather on the low side in the more acute stage of the illness. There was good neutrophilic response following operation.

factory and there was still slight discharge from the left meatus. On 3.11.36 temperature rose to 103° F. and stools were loose. Both wounds looked satisfactory, the right being almost healed. There was slight discharge from the right ear. On 9.11.36 the child was apyrexial but weight was stationary. On 23.11.36 the infant was gaining weight steadily, both wounds were healed, but there was still slight left otorrhoea. Condition continued satisfactory until discharge from hospital on 5.1.37.

INVESTIGATIONS.

Swabs : Nose—Staph. aureus.
Throat—Staph. and diphtheroids.
Right ear—Staph. albus.
Left Ear—Staph. and pneumococci.
Operative swabs : sterile.
Urine : faint trace of albumin, occasional red cells.
Faeces : no pathological organisms.
Blood culture : negative.
Mantoux reaction : negative.

Case 2.

W. S., male, aged 2 months, was admitted on 4.10.36 and discharged on 20.1.37.

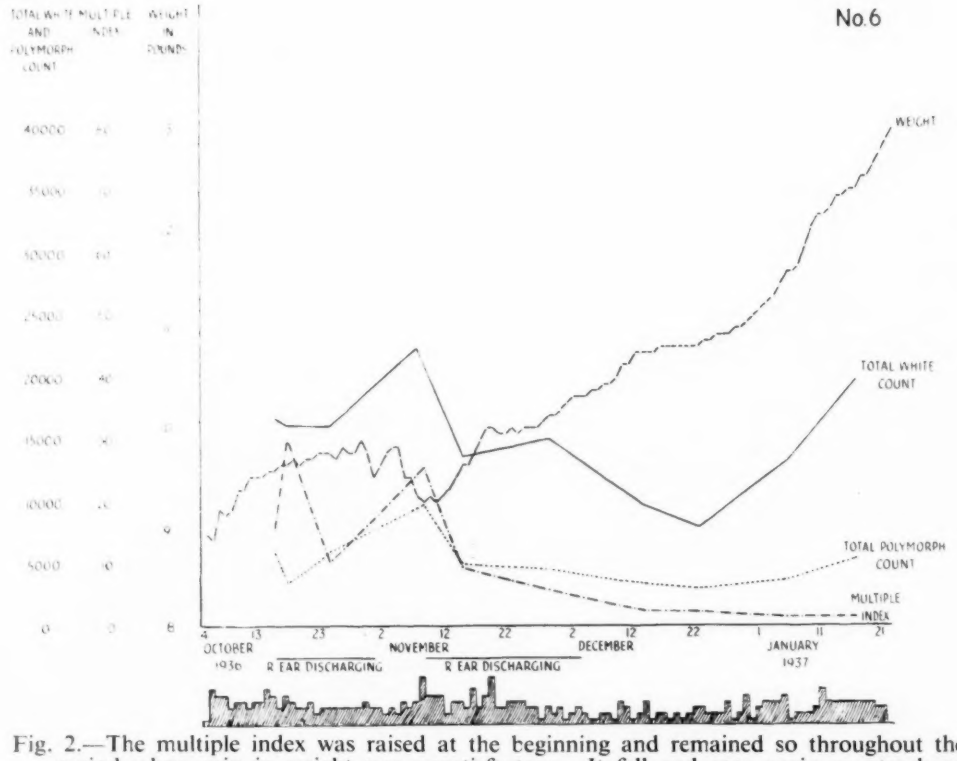

Fig. 2.—The multiple index was raised at the beginning and remained so throughout the period when gain in weight was unsatisfactory. It fell and rose again as otorrhoea ceased and weight fell. It fell again on 14.11.36 and continued to do so until it became normal and from that date weight began to go up—the two curves diverged. The total white count was not high to begin with when the multiple index was a more accurate guide, and its rise preceded the rise of total white count on 8.11.36. The total white count was actually rising when the child was discharged but the multiple index was normal and it was considered safe to discharge the infant. Throughout, the multiple index reflected the clinical condition of the child much more accurately than the total white count or total polymorphonuclear count.

HISTORY. This child had refused feeds for one week and vomited for three days. He was not unduly fretful, but stools were loose and there was some loss of weight.

CONDITION ON EXAMINATION. Left tympanic membrane was red but otherwise examination was negative. Temperature was 99° F. and stools very loose and frequent.

PROGRESS. Temperature subsided but stools continued loose and child did not gain weight satisfactorily. On 15.10.36 there was copious right otorrhoea with an injected tympanic membrane. Left tympanic membrane was slightly injected but there was no bulging. On 28.10.36 general condition was better, the stools had improved, but gain in weight was unsatisfactory. Right tympanic membrane was slightly injected but there was no discharge. On 4.11.36 weight loss began and temperature rose to 99° F. and on 7.11.36 right ear was again discharging profusely. Discharge continued for some time and weight gain continued. On 21.12.36 tympanic membranes were lustreless with no discharge and general condition was much improved. General condition then improved until discharge from hospital on 20.1.37.

INVESTIGATIONS.

Swabs : Nose and throat—Staph., pneumococci and M. catarrhalis.
Right ear—pneumococci.
Urine : faint trace of albumin.
Faeces : B. Morgan I.
Blood culture : negative.
Mantoux reaction : negative.

Case 3.

B. N., male, aged 4½ months, was admitted on 6.11.36, and discharged on 1.1.37.

HISTORY. This child had a history of screaming and putting its hand to its right ear, vomiting, not gaining weight satisfactorily, loose stools and restlessness.

CONDITION ON EXAMINATION. Left and right tympanic membranes were full and red posteriorly. Other examination was negative and the temperature was not elevated.

PROGRESS. A few days later child was gaining weight with temperature still normal. The left tympanic membrane was red and bulging and there was profuse discharge. The right tympanic membrane was red. On 20.11.36 weight-loss began and on 24.11.36 temperature rose to 99·8° F., the child looked ill and toxic, and passed loose stools. The left tympanic membrane was reddened posteriorly with slight bulging. Myringotomy was performed but no pus obtained. On 29.11.36 there was slight discharge from the left ear and pyrexia was still present. On 30.11.36 left myringotomy was repeated and a small quantity of thick pus obtained. On 3.12.36 temperature was 100·8° F. and the left ear was discharging and meanwhile weight had been unsatisfactory. By 11.12.36 general condition was much better, the tympanic membranes were just slightly pink and there was no discharge. The child's condition then gradually improved until it was discharged from hospital on 1.1.37.

INVESTIGATIONS.

Swabs : Nose—Staph. and diphtheroids.
Throat—Staph. alb., M. catarrhalis and pneumococci.
Right ear— } Staph. albus.
Left ear — }
Urine : faint trace of albumin.
Faeces : B. Morgan I & V.
Blood culture : negative.
Mantoux reaction : negative.

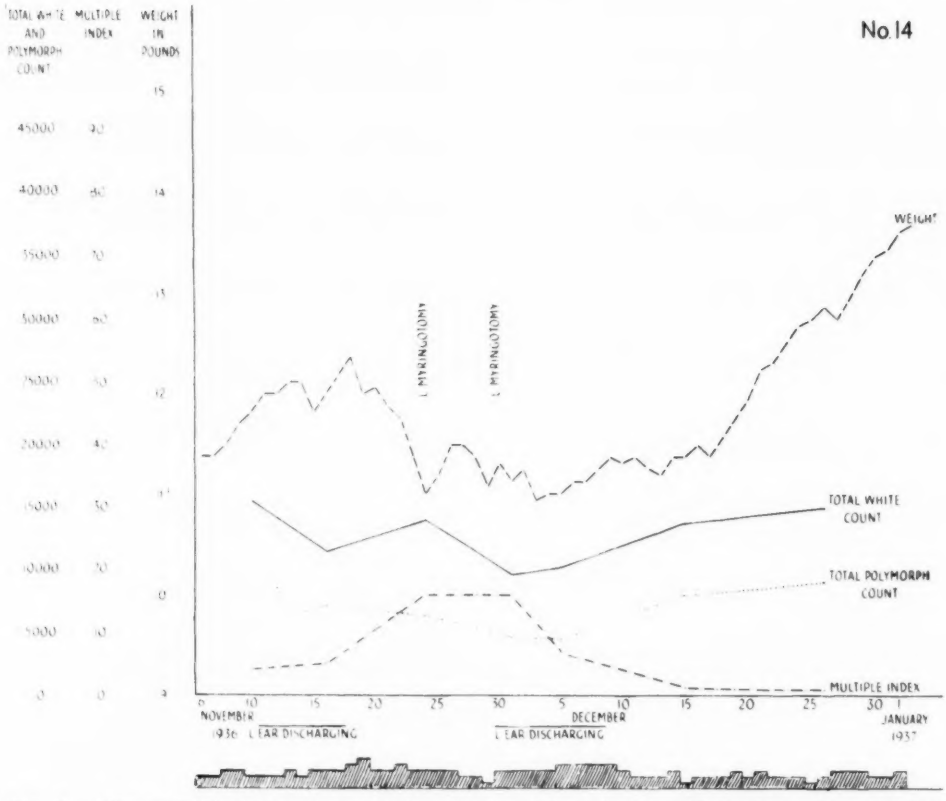

Fig. 3.—The multiple index was raised to begin with and rose still further when otorrhoea ceased. This rise coincided with a marked weight loss when the child was very ill. After drainage had been re-established the multiple index fell and at that point weight began to go up. The weight curves and multiple index curve converge during the ill period and diverge as the child recovered. The total white count was never outside normal limits, i.e. the multiple index was a much more accurate guide as to the infant's condition.

Case 4.

B. B., male, aged 8 months, was admitted on 21.11.36, and discharged on 8.1.37.

HISTORY. This child had had a 'cold' four days previously. He was drowsy and would not take his feeds. Vomiting occurred but no diarrhoea. Temperature was 103° F.

CONDITION ON EXAMINATION. He was a large, well-nourished boy. Throat was slightly injected and there were a few moist sounds at both bases. The tympanic membranes seemed normal.

PROGRESS. On the following day there was some nasal discharge, but otherwise his condition was unchanged. On the 22.11.36 the left tympanic membrane was red and bulging and the right tympanic membrane was injected, and on 25.11.36 bilateral myringotomy was performed and pus released from both ears. On 30.11.36 weight-loss began, the left ear was discharging profusely, and the right tympanic membrane was red and slightly swollen. On 5.12.36 considerable weight had been lost and the child looked toxic and restless. Bilateral myringotomy was again performed, drainage being unsatisfactory from the left ear, and pus was released. On 8.12.36 further loss of weight occurred and temperature rose to 103° F. On 9.12.36 left myringotomy

wound was re-opened and pus obtained, right myringotomy was repeated, but no pus found. On 10.12.36 temperature was normal but stools were loose, the child was very toxic and further weight loss occurred. There was slight discharge from the right ear. Until 14.12.36 the child remained very ill and left myringotomy was repeated, but no pus obtained. On 21.12.36 the child was gaining weight steadily, taking feeds well and its tympanic membranes were only slightly injected. This satisfactory state of affairs continued until 8.1.37 when the parents took the child home on their own responsibility although it was not quite ready for discharge from hospital.

INVESTIGATIONS.

Swabs : Nose—M. catarrhalis, diphtheroids and pneumococci.
Throat—negative.
Right ear— } Staph. aureus.
Left ear — }

Urine : negative.
Faeces : negative.
Blood culture : negative.
Mantoux reaction : negative.

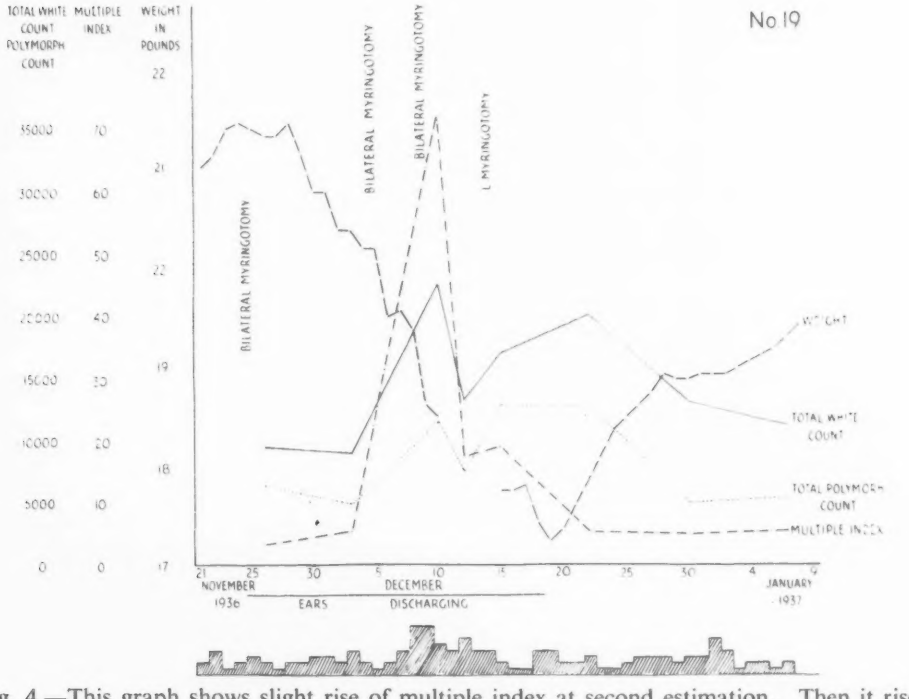

Fig. 4.—This graph shows slight rise of multiple index at second estimation. Then it rises very rapidly with the correspondingly marked loss of weight. At this point the weight and multiple index curves converge—indicating bad prognosis. Only after the third myringotomy when infection was overcome, does the multiple index curve fall. Simultaneously with its fall the weight curve begins to rise (giving divergence of the two curves), indicating a good prognosis. The multiple index was not normal when the child was taken out by its parents. The multiple index throughout gave a much more accurate estimation of the child's condition than the total white count or total polymorphonuclear count.

Case 5.

A. C., male, aged 9 weeks, was admitted on 5.11.36, and died on 1.12.36.

HISTORY. There had been right otorrhoea for one week and left otorrhoea for one day before admission. Stools had been loose and offensive for one week, gain in weight unsatisfactory and feeds not taken well.

CONDITION ON EXAMINATION. He was a small, thin baby, not dehydrated, with normal tension of the anterior fontanelle. There was purulent discharge from both ears. Other examination was negative and temperature not elevated.

PROGRESS. For the next fortnight slow gain in weight occurred and both ears continued to discharge profusely. On 19.11.36 there was a rise of temperature to 99·9° F. accompanied by marked loss of weight, the discharge from the ears having ceased. Bilateral myringotomy was performed and thick pus liberated from the left ear. Five days later discharge had again ceased and weight was stationary. Bilateral myringotomy was performed and again pus was obtained from the left ear. There was mild pyrexia—99·2°–99° F. On

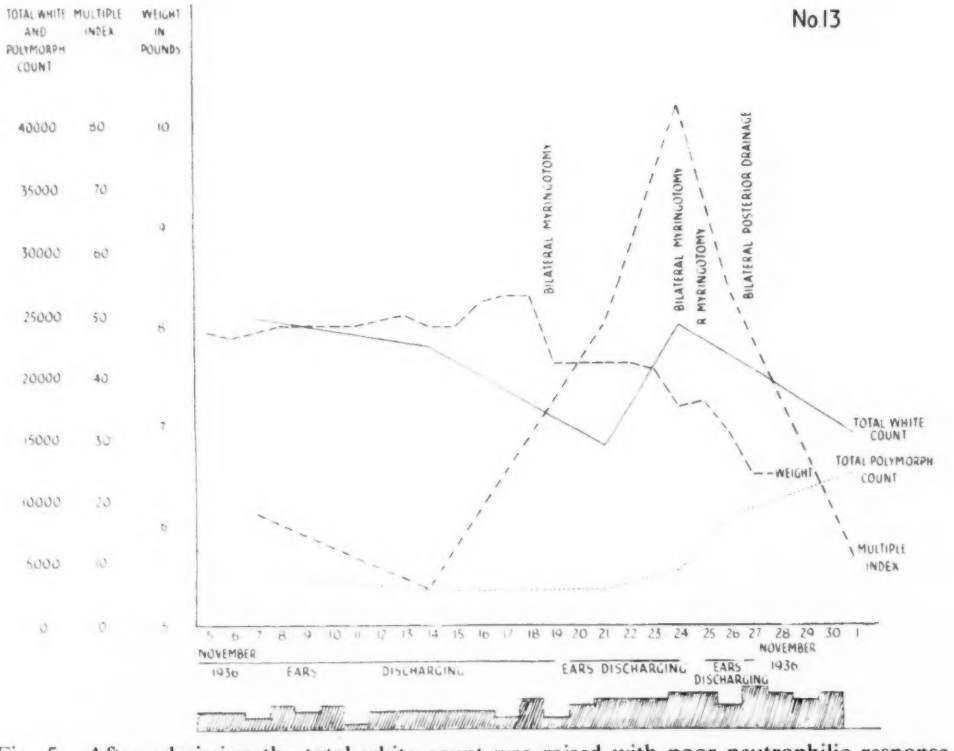

Fig. 5.—After admission the total white count was raised with poor neutrophilic response and the multiple index was raised. All three had fallen at the second estimation and the infant had gained in weight slightly. At the third estimation the multiple index had risen considerably while the total white count had fallen, thus giving an earlier and more accurate prognosis. After the myringotomies when the ears were discharging again, the multiple index fell somewhat. The last terminal fall of multiple index is probably due to marrow failure. The weight curve and multiple index curves converge, indicating a bad prognosis.

the following day right myringotomy was performed and slight amount of pus obtained. The infant's condition remained unsatisfactory and on 27.11.36 bilateral posterior drainage was performed and pus found in both mastoid cells. The child unfortunately died the following day.

INVESTIGATIONS.

Swabs : Nose—M. catarrhalis, pneumococci.
Throat—M. catarrhalis, Staph. and pneumococci.
Right ear—Staph. aureus.
Left ear—C. diphtheriae.

Urine : negative.
Faeces : B. Morgan I.
Blood culture : negative.
Mantoux reaction : negative.

POST-MORTEM. The right mastoid antrum was well drained at operation, but on the left side the bone was unhealthy and the antrum contained pus. The large intestine was distended and slightly injected, the kidneys were pale and toxic and the right lung showed some basal congestion. Other examination was negative.

Case 6.

B. S., male, aged 8 months, was admitted on 6.4.37, and discharged on 5.5.37.

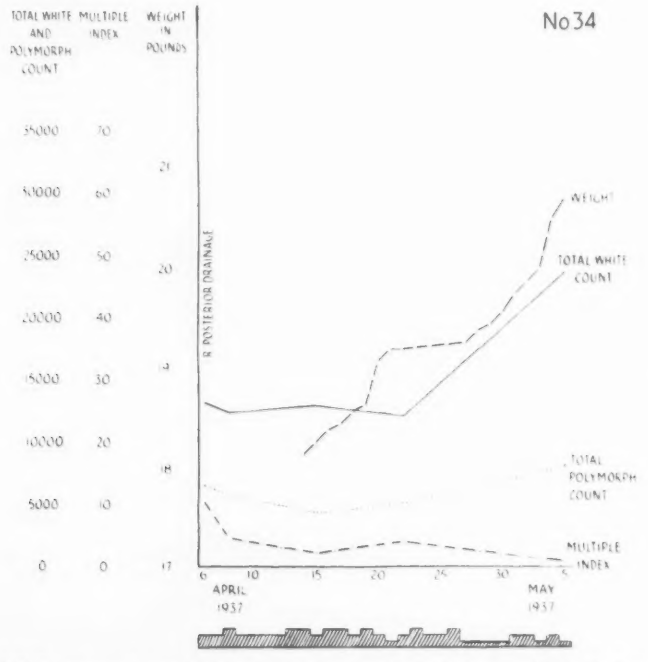

Fig. 6.—This child's general condition was very good and the multiple index, not markedly elevated, fell after the operation. The multiple index rose slightly on 22.4.37 with the abscesses on the scalp and fell gradually to normal. Gain in weight was progressive. The total white count was not raised at first but had actually risen at the end. The child was nevertheless discharged and there were no untoward developments. The multiple index here was an accurate guide to the clinical state and the curve illustrates the comparatively mild disturbance which occurs in cases of classical mastoiditis which is in accord with the clinical state of this infant.

HISTORY. For one week there had been a tender swelling behind the right ear which the infant would not allow its mother to touch.

CONDITION ON EXAMINATION. This was a well-nourished infant with swelling, redness and tenderness over the right mastoid process. The right

tympanic membrane was injected and bulging posteriorly. The left tympanic membrane was slightly injected. Other examination was negative and temperature was 99° F.

PROGRESS. On the evening of admission right posterior drainage was performed and pus found sub-periosteally. The bone was necrotic. Four days later condition was satisfactory. Gain in weight began and discharge lessened. On 23.4.37, when the child was almost fit for discharge, temperature rose to 100·2° F. and several small abscesses occurred on scalp These recovered satisfactorily and the infant was discharged well on 5.5.37.

INVESTIGATIONS.

Swabs : Nose—Staph., strep. and diphtheroids.
Throat—Pneumococci II.
Operation—Staph. albus.
Urine : faint trace of albumin.
Faeces : negative.
Blood culture : negative.
Mantoux reaction : negative.

Case 7.

A. L., female, aged 9 weeks, was admitted on 29.4.37, and died on 16.5.37.

HISTORY. This child had had right otorrhoea for two weeks. Three days before admission a swelling developed behind the right ear and then the left ear commenced to discharge. Some vomiting had occurred but no diarrhoea and gain in weight had been satisfactory.

CONDITION ON EXAMINATION. This was a fretful child in fair condition. There was redness, tenderness and swelling over the right mastoid process. The right tympanic membrane was acutely inflamed and there was profuse thick discharge. The left tympanic membrane was also reddened posteriorly and there was profuse discharge. Temperature was not elevated.

PROGRESS. Right posterior drainage was performed and pus was found subperiosteally. Operation on the left ear was contemplated but unfortunately not performed. Temperature rose after operation to 99·6° F. but rapidly subsided. On 8.5.37 the child's condition was very satisfactory but the left ear was discharging profusely. On 12.5.37 the child looked ill, the temperature rose to 101·2° F. and stools became loose. Left otorrhoea ceased on 12.5.37 and left myringotomy was without result. This pyrexia continued until the end and the child became very ill and toxic. The infant ultimately died on 16.5.37.

INVESTIGATIONS.

Swabs : Nose—Staph. albus.
Throat—Staph. albus.
Right ear—Staph. albus.
Left ear—Staph. and streptococci.
Operation (right Mastoid)—Staph. albus.
Post-mortem (left Mastoid)—streptococci.
Urine : not obtained.
Faeces : negative.
Blood culture : negative.
Mantoux reaction : negative.

POST-MORTEM. This was a case of right classical mastoiditis and unfortunately only a partial post-mortem was allowed. The right mastoid antrum was satisfactorily drained at operation. On the left side there was no external evidence of mastoiditis but when an incision was made over the mastoid process a commencing subperiosteal abscess was discovered with a sinus, through

which a probe could be put, leading into the mastoid antrum which was full of pus. There was also pus in the left middle ear. Examination of the rest of the body was not permitted.

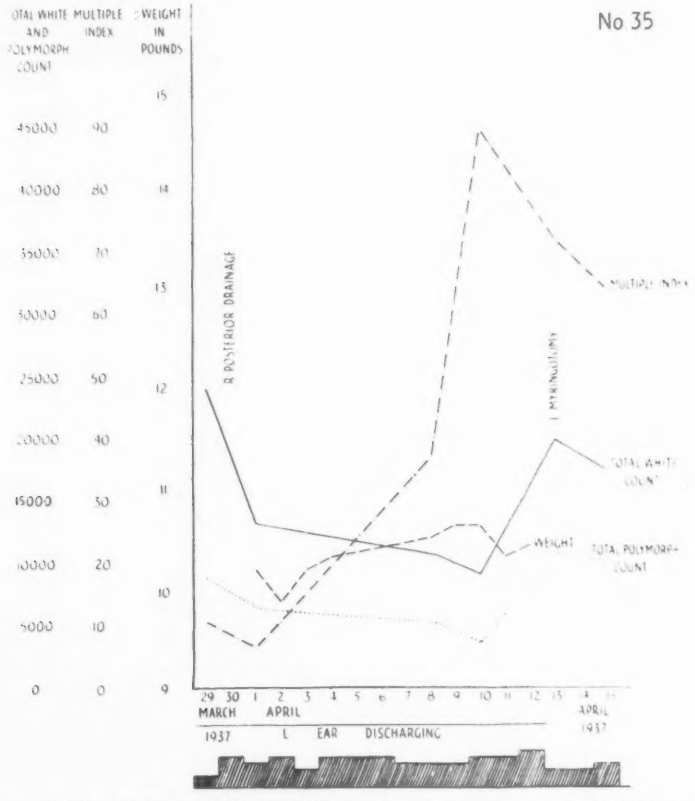

Fig. 7.—The multiple index was elevated but not markedly so on admission and fell after the operation. On 8.5.37 the multiple index had risen sharply and continued to do so until 10.5.37, during which time the child's condition appeared satisfactory. On 12.5.37 the infant became very ill, i.e. the rise in the multiple index preceded the onset of the acute illness by at least a week. The total white count gave no indication of this occurrence. It is also probable that it was the infant's left mastoid which caused its death, and that if it had also been operated on the fatal issue might have been averted. The fall in the multiple index towards the end was probably due to marrow failure. The multiple index throughout this case gave a clear index of prognosis and the progress of this infant's illness.

Discussion

In an attempt to analyse the many blood counts performed, the cases were divided into the following clinical groups :—

A. Mild cases without toxicity or dehydration, e.g. cases 1 and 2.

B. Cases, toxic on admission, and proved either at operation or post-mortem to have latent mastoiditis.

C. Cases, toxic on admission, with otitis media but never shown to have latent mastoiditis.

D. Cases which became toxic in hospital, proved to have latent mastoiditis (maximum readings at height of toxicity), e.g. cases 3, 5 and 7.

E. Cases which became toxic in hospital, with otitis media only (maximum readings at height of toxicity), e.g. case 6.

F. Cases presenting the classical picture of mastoiditis, e.g. cases 6 and 7.

Averages have been calculated of the first three estimations made in groups A, B, C and F. In groups D and E the average of the reading taken at the height of the toxicity has been calculated. These averages are recorded in the following tables :—

GROUP	FIRST ESTIMATION			SECOND ESTIMATION			THIRD ESTIMATION		
	TOTAL WHITE COUNT	TOTAL POLY-MORPH. COUNT	MUL-TIPLE INDEX	TOTAL WHITE COUNT	TOTAL POLY-MORPH. COUNT	MUL-TIPLE INDEX	TOTAL WHITE COUNT	TOTAL POLY-MORPH. COUNT	MUL-TIPLE INDEX
A	14,700	5156	11·5	14,200	4847	14·4	14,400	5685	7·3
B	19,400	8297	45·5	19,300	10,652	28·3	26,400	16,161	26·2
C	17,200	6997	21·1	17,400	8727	12·8	19,300	11,703	6·1
F	22,000	10,220	6·5	16,600	7029	4·0	15,200	6274	2·2

GROUP	MAXIMUM READING AT HEIGHT OF TOXICITY		
	TOTAL WHITE COUNT	TOTAL POLYMORPH. COUNT	MULTIPLE INDEX
D	17,100	5890	47·4
E	15,800	8515	38·9

These tables show that in group A (mild cases) the average total white count remains about the level of a high normal with a not unduly raised multiple index which falls. In the other groups the average total white counts are elevated but not in such a way as to be of diagnostic help. In group B (toxic cases of proved mastoiditis) the average multiple index is about four times as high as in the mild cases and shows a sustained elevation, while in group C (toxic cases of otitis media only) the average multiple index is about twice as high as in mild cases and shows gradual improvement. The cases which became toxic while in hospital show a high average multiple index at the height of the toxicity, those with otitis media only being slightly lower than those with mastoiditis. The cases of classical mastoiditis (group F) show an average multiple index about half that in the mild cases with gradual improvement. While a close scrutiny of the tables from which the average figures given were calculated would reveal exceptions to these averages, it is suggested that the height of the multiple index may be of some diagnostic significance, taken, as it always must be, in conjunction with the clinical findings and the clinical condition of the child. The height of the multiple index is of no value in selecting an optimum time to operate as degree of response varies from infant to infant. For instance, in case 2 several small scalp abscesses caused a rise of multiple index to 4·0, while in another case, not described in this paper, bilateral styes caused a rise to 89·6. In another case the infant suffered from acute non-

perforative otitis media and was never severely ill, but its multiple index was as high as 75·2. The value of the multiple index in prognosis can be seen from the accompanying graphs.

Conclusions

(1) Ordinary white counts and differential counts are of no value in prognosis or differential diagnosis.

(2) Analysis of the polymorphonuclear cells, on the lines suggested by Schilling and others, is applicable to infants of this age group.

(3) The use of some index of ' left shift ' such as the multiple index employed in the present series, is possibly of diagnostic value and certainly of prognostic value.

(4) Single counts are not nearly so useful as a series of estimations.

(5) The height of the multiple index is of no value as an indication of when to operate, for each infant's response to its infection varies and such counts must always be considered in conjunction with the clinical condition.

(6) An infant's weight has long been regarded as a good indication of its progress, and the manner in which the multiple index rises with loss of weight and falls with gain in weight is quite striking. As the multiple index and kindred indices are established as reliable indices of infection somewhere in the body, and as the multiple index in the present series fell and rose according to the success or non-success of treatment directed against the aural infection, it seems reasonable to conclude that the aural infection was the immediate cause of the infant's illness.

Thanks are due to Dr. W. E. Crosbie, Medical Superintendent, Alder Hey Children's Hospital, for permission to publish this work, and to Dr. N. B. Capon for his advice and criticism.

References

Alden, A. M., and Demotte, J. A. (1931). *Ann. Otol., St. Louis*, **40**, 95.
Arneth, J. (1904). *Dtsch. med. Wschr.*, **30**, 54.
Boies, L. R. (1931). *Arch. Otolaryng., Chicago*, **13**, 159.
Crocker, W. J., and Valentine, E. H. (1934). *J. Lab. clin. Med.*, **20**, 172.
Darling, J. F. (1908). *Edinb. med. J.*, **25**, 125.
Dench, E. B. (1908). *Laryngoscope, St. Louis*, **18**, 958.
Fletcher, E. G., and Mitchell, A. G. (1927). *Amer. J. Dis. Child.*, **34**, 807.
Gale, C. K. (1928). *Laryngoscope, St. Louis*, **38**, 538.
Japha, A. (1900). *Jhrb. Kinderheilk*, **52**, 242.
Klenerman, P. (1934). *Arch. Dis. Childh.*, **6**, 343.
Martin, A. T., and Ellenberg, S. J. (1935). *Arch. Pediat.*, **41**, 285.
McConkey, G., and Couper, E. C. R. (1938). *Arch. Dis. Childh.*, **13**, 137.
Mitchell. A. G. (1915). *Amer. J. Dis. Child.*, **9**, 358.
Ockel, G. (1924). *Arch. Kinderheilk.*, **75**, 40.
Rogatz, J. L. (1930). *Amer. J. Dis. Child.*, **6**, 70.
Rosenwasser, H., and Rosenthal, N. (1931). *Arch. Otolaryng., Chicago*, **14**, 291.
Sabin, F. R., Cunningham, R. S., Doan, C. A., and Kindwall, J. A. (1925). *Johns Hopk. Hosp. Bull.*, **37**, 14.
Schilling, V. (1929). *The blood picture and its clinical significance*. Trans. by R. B. H. Gradwohl, London.
Schüssler, E. (1924). *Jhrb. Kinderheilk.*, **104**, 87.
Washburn, A. H. (1934). *Amer. J. Dis. Child.*, **47**, 993.
—— (1935). *Ibid.*, **50**, 395, 413.
Weiss, A. (1931). *Arch. Otolaryng., Chicago*, **13**, 647.

STOMATITIS IN CHILDHOOD

BY

CLIFFORD G. PARSONS, M.D., M.R.C.P.*

Stomatitis is a common complaint which is usually considered to run a benign course, although Ebbs (1938) has suggested that during infancy certain forms of the disease may have serious consequences. An attempt has been made to throw further light on the matter by the study of one-hundred-and-fifteen children suffering from stomatitis who attended the Casualty Department of the Children's Hospital, Birmingham, between August 12 and December 14, 1938.

The term stomatitis means an ' inflammation of the mucous membrane of the mouth ' (Stedman, 1936), and many varieties of the disease have been described. Amongst the terms in more or less common use are the following : aphthous (follicular, herpetic, vesicular) stomatitis ; catarrhal (simple) stomatitis ; mycotic (parasitic) stomatitis or thrush ; ulcerative stomatitis (infective, Vincent's ulcero-membranous, necrotic or infectious gingivo-stomatitis) ; gangrenous stomatitis or noma ; and symptomatic stomatitis such as occurs in acute leukaemia and scurvy. It has been found that it is not always possible to classify the cases according to these groups, but it seemed that as a rule the clinical and bacteriological features of stomatitis in children under the age of two differ from those of older children. The cases have therefore been grouped according to age.

Sixty-seven of the 115 children were girls. The youngest patient was thirteen days old, the oldest eleven years. Over half of the cases occurred before the age of two years, and four-fifths before the third birthday, the incidence of the disease diminishing progressively as age increased.

Children under two years of age (67 cases)

History. When taking the history certain specific enquiries were made to ensure uniformity, but the use of leading questions was carefully avoided. The children had been ill for an average of 7·7 days, and one baby's mouth had been sore for six weeks before medical advice was sought.

' White mouth ' was apparently well recognized by the mothers as a cause of minor upsets, and the majority noticed ' something wrong with her mouth,' ' the white mouth,' or ' ulcers on the tongue ' as the earliest sign of anything wrong. It is possible that failure to take feeds readily, or excessive dribbling,

* Work undertaken during the tenure of a Hills' Scholarship, University of Birmingham.

drew attention to the local lesion. The presenting symptoms are shown as follows ; in some cases two symptoms were noticed simultaneously :—

Sore mouth, 24 cases ; Malaise, 14 cases ; Vomiting, 13 cases ; Anorexia, 10 cases ; Diarrhoea, 9 cases ; Earache, 2 cases ; Swollen glands, 2 cases ; Fever, 1 case.

One child, whose first symptom was swelling of the cervical glands, had been under observation for ten days before the oral infection became apparent, and in the meantime, the reason for the considerable glandular enlargement had remained a mystery.

By the time the children were first seen at hospital no less than fifty-five of the mothers had observed the stomatitis, although they did not all look upon it as important, and at this stage most of the children were restless, peevish and prone to cry. Many slept badly ; a few were drowsy. Anorexia was practically invariable, and was probably due to pain, since a number of the infants cried or refused to suck when offered food, and, to the complete bewilderment of their parents, failed to be pacified by a dummy. The fact that some of the patients were constantly dribbling saliva suggested that there was also discomfort on swallowing.

Thirty-six of the children had vomited before they were brought for treatment, twenty-one had numerous relaxed stools, and seventeen of the remaining children were constipated. A normal bowel habit was unusual. Unfortunately it was difficult to judge from the history whether alimentary disturbances predisposed to, or were the result of, oral infection ; on fifteen occasions a sore mouth was said to have preceded an attack of gastro-enteritis, and in seventeen children the reverse was true.

The frequency of pyrexia was also rather difficult to estimate from the history alone, but thirty-one of the babies were reported to have been feverish, and this was often confirmed. The temperature rarely exceeded 101° F., and was more usually about 100° F. Although parents did not as a rule remark on the fact spontaneously, pallor had been noticed in about half the patients.

An attempt was also made to determine from the parent's story whether there were any factors which influenced the development of the disease. Sixteen children had had stomatitis on a previous occasion, and one infant was actually seen during two attacks separated by an interval of about three months. There seemed to be no reason to suspect dietetic deficiency as a cause of the condition, for there were only four instances in which neither orange juice nor cod-liver oil had been given, or in which there were signs suggestive of vitamin or other deficiency such as nutritional anaemia. Neither the nutrition of the child, nor the social grade from which it came appeared to affect the incidence of the disease. Teething was obviously to be expected at this age, and so could not be implicated. Indeed the only significant discovery was that, of thirty-six mothers who were questioned on this point, only one could claim that her baby had been given neither bottle nor dummy. One instance was known in which two infected children sucked the same dummy.

Contact with other children suffering from stomatitis or with adults afflicted

with sore throats or herpes labialis was recognized in eight cases, but it is interesting that no common infecting organism could be found in the mouths of those contacts from whom swabs were taken.

Examination. Some of the patients looked healthy and well, but most were tired, peevish and hollow eyed. A pinched face and a leaden grey colour, which was so characteristic that it allowed the diagnosis to be made at sight on more than one occasion, often implied that the baby also had gastro-enteritis. Ebbs (1938) described this curious colouring in cases of thrush oesophagitis. The lips were dry and sometimes excoriated from excessive dribbling, but herpetic and impetiginous lesions were exceptional.

Various kinds of stomatitis were encountered, and these may be described as follows :—

1. Pure thrush, in which there was ' exudate ' but little or no ulceration or inflammation. The mycelium either resembled milk curds, or was more granular, like a patch of damp table salt. It was found especially on the cheeks, but also on the palate or tongue, and was fairly easily removed with a swab, leaving a raw, or even a bleeding, surface. Enlargement and tenderness of the cervical glands was absent or minimal.

2. Aphthous stomatitis was characterized by the presence of small vesicles, or more usually shallow ulcers, of greyish-white colour, surrounded by a narrow but bright halo of inflammation. The ulcers were exquisitely tender to the touch, rarely measured more than two mm. in diameter, and were situated in order of frequency on the tongue, cheeks, the inner surface of the lips, the palate, and the fauces. There was sometimes slight enlargement, but rarely tenderness, of the glands.

3. A combination of the above two types was by far the commonest form of stomatitis met with in children under the age of two. On one or two occasions the tongue was literally covered with small aphthous ulcers, which gave the mouth a peculiar dusky cyanotic appearance ; mycelium was present on the cheeks ; gastro-enteritis was the rule, and in these cases the prognosis was hopeless.

Instead of aphthous ulcers there were sometimes irregular areas on the cheeks or tongue from which the superficial layer of mucous membrane had been stripped. The bases of these large ulcers were either clean, or covered with a yellowish-grey exudate.

4. Amongst the younger children the Vincent's type of stomatitis was seldom encountered in its fully developed form, but it was seen in older children and then presented the following characteristics. The gums were greatly inflamed, a dusky red colour, bleeding easily and extremely tender. They were swollen, turgid, bulging up between and around the teeth, which were inclined to be loose. The shallow pits in which the teeth appeared to lie were filled with yellowish debris. Ulcers, in the form of grey streaks parallel to and close to the gum margin, were sometimes seen. The breath was foul ; the tongue heavily furred ; the throat red, but not obviously infected ; and there was enlargement and tenderness of lymphatic glands, particularly of the submental, submaxillary and tonsillar groups.

5. Apthous ulceration occurring in combination with the above picture affected ten of the younger children. Incidentally it may be pointed out that the less the gingivitis and odour, the more closely did this variety of stomatitis resemble that described in section 3 above. Indeed, overlapping of clinical features made a hard-and-fast distinction between thrush, aphthous and Vincent's stomatitis impossible, although they are usually considered to be separate diseases. Bacteriological examination, which will be discussed later, likewise failed to help materially in a clear classification of the clinical types. In general, it can be said that in children under two the mycotic, mycotic-aphthous and aphthous forms of stomatitis predominated over the aphthous-Vincent or Vincent varieties.

Certain complications occurred with a frequency which implied that they were not merely coincidental. Severe gastro-enteritis was particularly important in this respect ; it was present in twenty-four cases and proved fatal in nine of these. Probably a tenth child also died, since he was in extremis when last seen, but had to be transferred to another institution, and so could not be followed. All of these ten babies had typical mycotic stomatitis, and thrush was cultured from the mouth. In two or three cases mycelium was also found in the stools, and in others thrush oesophagitis was demonstrated at autopsy. Six children had a napkin rash, but only one of these had gastro-enteritis ; seven cases were complicated by otitis media.

Bacteriology. Bacteriological examination was undertaken when the children first attended the department. An ordinary cotton covered throat swab was rubbed firmly over the affected area and was despatched immediately to the laboratory, where after a direct smear had been made on a clean glass slide, a plate of Sabouraud's medium was inoculated. It was found in practice that the significant organisms were usually revealed in the smear. Failure to demonstrate expected organisms, for example from cases of thrush which were quite typical clinically, may have been due to the practice of taking only a single swab in each instance.

Sixty children were examined bacteriologically, and of these forty-one showed the spores or mycelium of thrush. Thrush was the only organism obtained in pure culture (fifteen cases), and it was isolated from examples of all the clinical varieties of stomatitis, including eight of the ten cases of the aphthous-Vincent type. Thus the problem of classifying stomatitis clinically was reflected in an exactly similar difficulty from the bacteriological standpoint.

Other bacteria were found as follows :—

Staphylococci (aureus, albus or citreus) in twenty-six cases ; pneumococci in twenty-one cases ; streptococci (haemolytic, non-haemolytic or viridans) in eighteen cases ; micrococcus catarrhalis in sixteen cases ; unidentified cocci in four cases ; micrococcus tetragenus in one case. Bacillus fusiformis was isolated eight times, twice in association with spirochaetes and three times with thrush. Organisms met with less frequently were leptothrix, diphtheroids, bacillus Friedlanderi and influenzae (table 1).

Of twenty-four patients with well-marked symptoms of vomiting or diarrhoea, thirteen were found to have thrush, two had signs typical of thrush but no swab was taken, and swabs from the remainder showed neither spores nor mycelium. Material taken from aural discharges and from skin lesions of the buttocks or fingers failed to demonstrate a direct connexion between these and the stomatitis, although on other occasions at the Children's Hospital thrush has been cultured from the ear.

Blood counts. Blood, for examination of the white cells, was taken from thirty-one cases at the same time as the swab. The total number of leucocytes ranged from 4000 to 29,000, averaging about 14,000. There was some immaturity of the granulocytes, but the most striking alteration in the differential white cell count concerned the monocytes, which were present in numbers varying from 2 to 17 per cent. of the total count. In twenty-one of the thirty-one children examined, monocytes constituted 6 per cent. or more of the white cells, and in fourteen cases 10 per cent. or more.

This monocytosis was so characteristic that the haematologist, knowing nothing of the clinical history, was often able to make a diagnosis of stomatitis immediately he looked at the blood film. It was something of a surprise to discover that the blood changes appeared to have no connexion with the type or severity of the stomatitis, nor with the organism which caused it. For example, seven of the cases with a monocytosis of 10 per cent. or more had positive cultures for thrush, and seven negative cultures. Likewise no relationship could be traced between the blood findings and the presence or absence of complications such as gastro-enteritis.

Blood counts were repeated in some cases after the mouth was completely healed and the monocytosis was still present ; it is not known for how long the abnormality persisted. It may be mentioned in passing that during this period large numbers of blood films were being examined from children of the same ages, some healthy and others suffering from a variety of diseases, yet no comparable blood changes were encountered.

Treatment. Before the relative merits of different forms of treatment can be assessed, something must be known of the natural course of the disease in the untreated patient. Information on this point was gathered from the history, which gave the impression that the disease was not self-limited, since the children had been ill for an average period of a week, and in many cases for two or more weeks, before treatment was started.

As a further control certain children were treated with saline mouth washes only, and others with local applications of glycerin, borax and honey in different combinations, as these are the favourite remedies of parents, medical practitioners and clinics in the district. One child recovered during treatment with glycerin and borax, but no other patient in the control group improved until other therapy was instituted.

The efficiency of different kinds of treatment was measured by the time for which therapy had to be continued before the stomatitis was entirely healed. Healing was judged by a careful inspection of the mouth, since symptoms as a rule disappeared several days before the local signs.

As soon as the mouth was healthy treatment was stopped, but the patient was examined again a week later to ensure that cure was complete. This final visit enabled four mild relapses to be recognized, all of which responded immediately to further medication.

Treatment was for the most part entirely local. No specific alteration was made in the diet, but in one or two unselected cases a mixture containing potassium chlorate and iron perchloride was ordered. The mouth was painted daily with one of four different applications. Whenever possible this was carried out by nurses in the department, so that progress could be watched. The painting was done with a cotton wool swab wrapped round either a pair of forceps or the little finger, and special care was taken that no part of the mouth should escape attention. The four applications were : (1) 1 per cent. aqueous solution of gentian violet ; (2) novarsenobillon, 0·6 gm. dissolved in 6 c.c. of glycerin and 12 c.c. of water ; (3) 10 per cent. aqueous solution of sodium perborate ; (4) solution or tincture of merthiolate (Lilly). (The tincture was preferred as it was coloured, but no distinction has been drawn between the two in estimating results.) All solutions were freshly dispensed at intervals of about one week.

Fifty-nine cases were followed, but nine of these have been excluded from consideration, as they died from gastro-enteritis after the stomatitis had apparently responded satisfactorily to treatment. The average duration of therapy before cure was complete was 6·7 days for gentian violet and merthiolate, 7 days for N.A.B. and 10 days for perborate. One failure was experienced each with gentian violet and N.A.B. Symptoms were relieved rapidly, especially with merthiolate and gentian violet, and parents were delighted that often within twenty-four hours the appetite had returned, and restlessness and peevishness had disappeared.

Children over two years of age (48 cases)

History. Several children were seen on the day of onset, but on the average it was not until the fifth day that the patient first arrived at the hospital. One boy (excluded in calculating the average) had been ill, with remissions and exacerbations, for six months before advice was sought. The presenting symptoms, sometimes occurring in combination, were as follows :—

Sore mouth, 18 cases ; Malaise, 14 cases ; Anorexia, 11 cases ; Vomiting, 3 cases ; Sores on face, 3 cases ; Swollen cervical glands, 2 cases ; Odour of breath, 1 case ; Sore fingers, 1 case ; Earache, 1 case ; Sore throat, 1 case.

Listlessness, drowsiness, extreme irritability and general malaise were practically constant by the time that the child reached hospital. Headache, occasionally intensely severe, was a troublesome symptom in nineteen of the patients, and the parent's attention had been drawn to the mouth in all but three of the cases. The offensive odour of the breath, noticed by forty-one of the parents, apparently taxed their powers of description, for it was likened to an abscess, a lavatory, to 'something awful,' and to a drain. It is therefore not surprising

that nausea was often complained of by the patients. In eighteen cases there was vomiting. Constipation was usual, and diarrhoea was very uncommon.

There was usually a history of feverishness, and the temperature was generally higher than amongst the younger children, sometimes reaching 103° F. Twenty-eight of the mothers had noticed that their children were paler than normal ; complaint of sore throat was unusual.

Of thirty-eight patients who were asked, ten had had previous attacks of stomatitis. The type of stomatitis from which they had suffered in the past was often not known, but as it occurred in infancy it was probably thrush or aphthous ulceration. One child was said to have had three attacks of aphthous stomatitis.

As would be anticipated, dummy sucking was less prevalent amongst these older children, and was met with on only five occasions. One child with nutritional anaemia provided the only evidence of dietetic deficiency.

When two adults suffering respectively from peritonsillar abscess and herpes febrilis are included as possible sources of infection, contact could be established in nineteen of the forty-two cases in which the point was raised. Swabs were taken from six pairs of contacts, but no conclusions were possible from the results obtained.

Examination. The majority of children were pale, had a toxic appearance and were listless and miserable, but only two or three were sufficiently ill to necessitate in-patient treatment. The characteristic nauseating smell was common, and thirty-one of the patients had the Vincent's type of stomatitis already described. Aphthous ulcers or large irregular superficial erosions were often present in addition, particularly on the lips, tongue and cheeks ; the tongue was furred and the throat red, but tonsillitis was distinctly unusual. Enlargement of the regional lymph nodes was almost invariable (forty-three cases), and tenderness was noticed in about half the cases. Sometimes the glandular swelling was as great as that seen in the ' bull-neck ' of diphtheria. Suppuration occurred only once; it is rarely encountered as a result of stomatitis.

Ulceration with little or no gingivitis was also seen, but the pure mycotic or exudative lesion was not encountered. The ulcers were very tender, as certain members of the staff of the department can witness from personal experience.

Whilst several children had carious teeth, it is doubtful whether this played any part in the production of the stomatitis, although in one case the gingivitis apparently arose as a direct consequence of dental extraction.

The commonest complication, observed nineteen times, was a herpetic lesion affecting the lips and sometimes the nose, frequently secondarily infected and then resembling impetigo. Sore fingers or paronychiae were seen three times, and conjunctivitis twice ; both were probably a consequence of finger sucking. The spleen was enlarged sufficiently to be easily palpable in four children, whose ages ranged from two and a half to six years, and a fifth child had a generalized enlargement of the lymphatic glands which made it necessary to exclude a number of other possible diagnoses. Bronchitis and otitis media each complicated the disease on four occasions, and napkin rash was present once.

The development of erythema nodosum in two children whilst under treatment is interesting. One girl almost immediately afterwards developed signs of rheumatic carditis ; her mouth was infected with staphylococcus aureus haemolyticus. The other child had a tuberculous family history.

Bacteriology. Thrush was again the only organism found in pure culture and it was isolated from children up to the age of ten. The accompanying table 1 summarizes the bacteriological findings, and allows comparison with the children of the younger age group. It is apparent that just as there is a change in the clinical picture, so also the emphasis has passed from thrush to the anaerobic organisms associated with the Vincent type of infection. But despite this general agreement between clinical and bacteriological pictures, it was difficult to prophesy what organism would be found in any individual case.

TABLE 1

ORGANISM	IN 60 CASES UNDER 2 YEARS	IN 39 CASES OVER 2 YEARS
Thrush (Monilia albicans)	41	10
Bacillus fusiformis	8	24
Spirochaetae (Vincentii)	2	13
Staphylococcus (all types)	26	27
Streptococcus (all types)	18	14
Pneumococcus	21	14
Micrococcus catarrhalis	16	21
Other cocci	5	1
Leptothrix	7	18
Diphtheroid	5	5
H. Influenzae	6	3
Bacillus Friedlanderi	6	2
Other bacilli	0	2

Blood counts. The white cells of twenty-five children were counted, and the total number of leucocytes was found to vary between 5000 and 21,000, averaging about 12,000 per c.mm. There was some immaturity of the granular cells, and in one case there were 7 per cent. of eosinophils. Once again a monocytosis constituted the characteristic abnormality : these cells ranged from 0 to 14 per cent. of the total count, amounting to 6 per cent. or more of the leucocytes in seventeen cases, and 10 per cent. or more in six cases. Again no relationship could be found between the symptoms, signs, or infecting organism on the one hand and the monocytosis on the other.

Treatment. The methods of treatment, and the criteria for comparison, were the same as those used for the younger patients, and the average length of time in days before cure was complete, is set out in table 2.

TABLE 2

TYPE OF STOMATITIS	N.A.B.	PERBORATE	GENTIAN VIOLET	MERTHIOLATE
Vincent's type	8·1	9·7	6·9	7·3
(B. fusiformis in smear) ..	7·6	9·1	6·0	6·9
Aphthous type..	5·7	7·6	6·4	4·0*
(Thrush in smear)	7·0	12·0*	5·7	2·0*

* Average taken from two cases or less.

The impression gained was that there was little to choose between N.A.B., gentian violet and merthiolate, although symptoms appeared to be relieved less rapidly by N.A.B. than by the other two preparations, both of which often improved the appetite and general condition in quite a dramatic way. Two adults who developed aphthous ulceration during the course of the investigation were loud in their praises of gentian violet, which brought almost instantaneous freedom from pain. A few failures were encountered, two with gentian violet, and one each with merthiolate and N.A.B. There were no relapses when the course of treatment had once been completed.

Discussion

It was calculated that about 5 per cent. of patients passing through the department during the autumn of 1938 had stomatitis. As the great majority of these children were under the age of three, the proportion was considerably greater in this age group, and so constitutes a matter of social importance. The number of cases may perhaps have been influenced by an autumnal rise in the incidence of the disease (Black, 1938), but stomatitis is a common ailment at all times of the year. It is also possible that the numbers may have been swelled somewhat by children being referred from other departments, as the study was known to be in progress. In whatever way the numbers are accounted for, the fact remains that in four months 115 children were seen with stomatitis, and over half the cases were infected with thrush. This is particularly interesting since it is believed by many that thrush is on the wane. There seems no valid reason to suppose that thrush is more common in Birmingham than in other parts of the British Isles, although it is certainly commoner in this country than it is in the United States, where ' It is fair to say that . . . acute infectious gingivo-stomatitis occurs four or five times as often as all other specific types of acute stomatitis in infants and older children combined. Thrush and aphthous stomatitis come next in frequency.' (Black, 1938.)

A possible explanation of this difference, which has support from the evidence of this paper, is that the English dummy is seldom used in America. All of the cases of thrush oesophagitis described by Ebbs (1938) were artificially fed. If thrush is indeed associated with the bottle and dummy, and is so rare amongst the breast fed, then it is difficult to agree with Cassie (1938), who commenting on Spence's eulogy of breast feeding, remarks that artificial feeding is both easy and safe.

It is true that thrush, like other forms of stomatitis, is supposed to be a benign condition, but nevertheless nine, and probably ten, children of the present series died, and Ebbs has pointed out that monilia oesophagitis is frequently fatal. Unfortunately there was no material evidence to help to decide the relationship between thrush and gastro-enteritis. When treatment had once been instituted gastro-enteritis did not develop in any child with thrush, but the reverse phenomenon was seen on one or two occasions. Even so the conviction remains that thrush may cause vomiting. Moreover, in spite of the observation by Ebbs that diarrhoea is never an outstanding sign in thrush oesophagitis, the present study shows that it is often associated with mycotic

stomatitis. Since the mycelium has been shown to infiltrate the walls of the oesophagus and has been recovered from the stools of babies with diarrhoea, there is no doubt that the fungus may invade the intestinal tract, and it is not altogether unreasonable to assume that it may be the cause of the diarrhoea. Even if stomatitis is not responsible for the alimentary disturbance, association of the two conditions is exceedingly common, and the prognosis appears to be increasingly bad according to the severity of the mouth lesion.

The problem of etiology is an absorbing one. It has been pointed out that there is so much overlapping of both clinical and bacteriological characteristics that hard-and-fast division into the recognized types of stomatitis is impossible. This agrees with Black's (1938) opinion that ' many of the cases at one period or another could have been classified according to any one of thirty or more synonyms in more or less general use.' He holds, and the present study confirms his observation, that the ulcers of acute infectious gingivo-stomatitis cannot be distinguished from the lesions of aphthous stomatitis. On this evidence he concludes that the two conditions may have the same primary cause. It is apparent that exactly similar ulcers may also be associated with thrush, and this leads to the belief that aphthous ulceration is merely a symptom, and not a disease entity. If this were so it would be easy to understand the overlapping of clinical features.

With the exception of thrush, all the organisms which were isolated have been demonstrated in normal healthy mouths, and this supports the view that they are secondary invaders, although as such they may become pathogenic. The evidence also suggests that in younger children thrush may act as the primary cause of pure mycotic, aphthous, or even of Vincent's stomatitis, since it may provide the ground on which secondary invaders may become active.

If the child is over two thrush becomes less likely as the primary cause of stomatitis, and in these cases a virus may be responsible. It has been shown by Dodd and her colleagues (1938, 1939) that if material obtained from the buccal lesions is inoculated into the cornea of a rabbit, a kerato-conjunctivitis develops corresponding exactly with that produced by the herpes virus. Clinical support is given to this belief by Levine et al. (1939), who describe an epidemic of aphthous stomatitis with herpetic complications. This agrees with the observation in this study of the prevalence of herpes labialis in children of the older age group, and the development of two cases of stomatitis after contact with adults suffering from herpes febrilis. Further, when swabs were taken from contacts, in whom it would be expected that a common infecting organism might be demonstrated, no such organism could be found. If a virus is the primary cause of the stomatitis of older children second attacks will probably be rare, and Black (1938) maintains that this is so. A history of previous stomatitis was elicited from a large number of older children, but a good description of the nature of these earlier attacks was not obtained. As they developed during early childhood it is probable that they were due to thrush, and infection by monilia apparently does not confer immunity. One child was said to have had three attacks of aphthous stomatitis. Second attacks of stomatitis in later childhood were not encountered, perhaps because thrush is less common.

This may also account for the general differences in the form of stomatitis below and over the age of two.

There was no evidence to support the belief that stomatitis is due to dietetic deficiency. This corresponds with the view of several recent writers. Herlitz (1938), who investigated the vitamin C saturation of children with and without gingivitis, was unable to find any significant difference between the two groups. Similarly Topping and Fraser (1939) concluded that there was no definite relationship between the commoner mouth lesions and vitamin deficiency. The very fact that deficiencies of so many vitamins have been implicated as a cause of the disease is itself a point which throws doubt on their importance.

In neither age group did the disease appear to be self-limited as is the case in America, but local treatment brought about rapid relief of symptoms and speedy cure. Whilst there may be no rational use for the local application of N.A.B. (Black, 1938) this paint was certainly more effective than perborate. It might be argued that it was the glycerin in the application which was responsible for the results, but if this were so it would be difficult to explain the failure of glycerin and borax. The most impressive results were obtained from a 1 per cent. solution of gentian violet or from merthiolate. Both these paints are coloured and there is therefore no difficulty in telling whether the affected areas have been thoroughly treated. Gentian violet has the advantage that it is considerably cheaper than merthiolate. It is also non-toxic, and has been administered by mouth in doses of 60 minims, until the stools were stained, in an effort to kill mycelium in the oesophagus and gut of babies, without causing any toxic effects. Merthiolate may be safe when administered in similar doses, but the manufacturers did not encourage its use in this way. Mirvish (1938) has advocated the use of tannic acid jelly in infantile stomatitis and this preparation was employed in a few cases at the end of the study. An insufficient number of children was treated to enable this form of treatment to be compared with other methods, but on the whole gentian violet appeared to be more effective. The etiology and treatment of stomatitis was discussed recently at a meeting of the American Pediatric Society (1939). Smith and others pointed out that American dental surgeons have used chromium trioxide (chromic acid) as a local application with great success, and although the results do not seem to be any more satisfactory than those obtained with gentian violet, a trial of the method will be made when an opportunity arises. Abt was of the opinion that chromic acid had no effect on the duration of the disease, but agreed that it was a most soothing form of treatment.

The changes which were observed in the white cells have apparently not been described previously, although Peeney (1939) says that he has seen a similar monocytosis in adults afflicted with Vincent's stomatitis. Black (1938) noticed no change in the differential leucocyte count of the cases which he studied. The monocytosis is difficult to explain. It appeared to be specific for stomatitis and yet not for the type of stomatitis, the organisms isolated, the severity of the disease, nor its complications. Perhaps it might be used as an additional argument for the existence of an unrecognized primary cause for all these types of stomatitis.

Summary

A hundred and fifteen cases of stomatitis have been studied. Girls were affected more frequently than boys, and four-fifths of the cases were under three years of age.

A rough distinction was noticed between the stomatitis found under and over the age of two. The commonest presenting symptom in both groups was sore mouth, and anorexia and malaise were almost always present. Diarrhoea was common in children of the young group, constipation in the older children. Vomiting was frequent in all. Pyrexia was considerably higher in the older group. Toxic, greyish pallor, without obvious anaemia, was an exceedingly common symptom.

Stomatitis in young children occurred in the artificially fed, or those who sucked dummies. It was usually due to thrush, even when aphthous ulceration was the chief sign. There was little or no odour and the cervical glands were not involved. Gastro-enteritis was an extremely serious complication. There was no distinct division between this type of stomatitis and the one occurring in older children.

The stomatitis of older children was of the Vincent type, but was often complicated by aphthous ulceration, whilst inflammation, offensive odour, and glandular enlargement were the rule. The organisms concerned were anaerobes, but an underlying organism of unknown character, possibly a virus, was probably the cause, and aphthous ulceration merely a symptom.

An absolute and relative monocytosis was found in many cases of stomatitis in all age groups. It was quite characteristic but the reason for its occurrence is unknown.

Various forms of treatment were tried, and local application of either 1 per cent. aqueous solution of gentian violet, or tincture of merthiolate (Lilly) were most effective. Symptomatic relief was particularly rapid. There was no evidence to implicate vitamin deficiency as playing any part in the condition.

Acknowledgements are due to Dr. J. H. Ebbs who suggested this line of study, and who, with the help of Dr. A. Dennison carried out the haematological and bacteriological investigations ; and to Messrs. Eli Lilly & Co., Ltd., who provided the supplies of merthiolate.

References

American Pediatric Society. Discussion (1939). *Amer. J. Dis. Child.*, **58,** 907.
Black, W. C. (1938). *Ibid.*, **56,** 126.
Cassie, E. (1938). *Lancet*, **2,** 432.
Dodd, K., Johnston, L. M., and Buddingh, G. J. (1938). *J. Pediat.*, **12,** 95.
——, ——, —— (1939). *Amer. J. Dis. Child.*, **58,** 907.
Ebbs, J. H. (1938). *Arch. Dis. Childh.*, **13,** 211.
Herlitz, C. W. (1938). *Acta Paediatr., Stockh.*, **23,** 43.
Levine, H. D., Hoer, S. O., and Allanson, J. C. (1939). *J. Amer. med. Ass.*, **112,** 2020.
Mirvish, I. (1938). *Lancet*, **2,** 1292.
Peeney, A. P. (1939). *Personal communication.*
Stedman, T. L. (1936). *Practical Medical Dictionary, London.*
Topping, N. H., and Fraser, H. F. (1939). *Pub. Health Rep., Washington*, **54,** 416.

STAPHYLOCOCCUS AUREUS INFECTION OF THE LONG BONES IN THE NEWLY BORN

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In a study of the clinical picture and effects of various infections in the new-born there have occurred three cases of staphylococcal infection of the long bones. These are here reported and discussed because so little has been written on the subject, and also because they illustrate how this disease process, like many others, differs in its clinical picture and results in infancy from a similar process in later childhood.

In 1935 Dilliehunt made some observations on osteomyelitis in infancy, and pointed out that the condition is locally relatively benign in infants under two years of age. He reported two cases in which the onset had been before the age of one month. In one case there was a staphylococcus aureus infection of ten days' duration of the lower end of the femur. The temperature was 102° F. on admission, but, judging from the photograph, the child was not wasted or ill. In the other case a streptococcal infection of the patella was present. The temperature was 102° on admission and the child was markedly malnourished, with a dry skin, after ten days' illness. Both cases were treated with simple incision down to the abscess, and recovery was rapid and complete. There was no evidence of disease five weeks after operation.

In the same year Green stressed the differences between osteomyelitis as it occurs in infancy and in older children. He attributed the rapid healing of the bones and the absence of sequestra in infancy to the thinness of the cortex and loose attachment of the periosteum at this age, the pus thereby escaping easily and rapidly from the medulla into the soft tissues without causing any necrosis of the cortex. For this reason he advocated treatment of the infant first and of the local condition later, and suggested that the less done at operation the better. He stated that by giving the infant fluids and immobilizing the affected limb until the general condition was satisfactory, and then making a simple incision down to the pus without disturbing the bone, he had treated thirty consecutive cases under two years of age with only two deaths, both of which were in infants under two months of age with diffuse sepsis.

In 1933 Dunham reported thirty-nine cases of septicaemia in the new-born, in four of which osteomyelitis was present. One was a fatal case of staphylococcal infection with multiple bony lesions in addition to peritonitis, pneumonia, meningitis and multiple skin abscesses. One was a case of staphylococcal osteomyelitis of the femur in which the general condition was satisfactory at first, but open operation was followed by erysipelas-like lesions around the wound, streptococcal septicaemia, and death. A case of bacillus coli infection of the upper end of the humerus was treated without operation and recovered. A case of mixed bacillus pyocyaneus and staphylococcus aureus infection of the clavicle and sternoclavicular joint died without operation.

* In receipt of a Medical Research Council Fellowship.

Mount (1935) reported a case of haemolytic staphylococcal septicaemia with suppuration in the left elbow joint and around the lower end of the left humerus, and pneumonia. Death occurred at the age of fourteen days after only two days' illness.

Case reports

Case 1. R. C. : This was a male child born at term in a maternity hospital on September 10, 1937. Birth weight was 7 pounds 14 ounces. The delivery and puerperium were normal and the child was not known to have been in contact with any infection. The child was breast fed for ten days and then weaned. The mother stated that the umbilicus was a little moist at the tenth day. Slight redness of the left knee was noticed a few days later, and rapidly

FIG. 1.—Case 1. R. C. X-ray of left knee, October 22, 1937, showing osteitis of lower end of left femur.

FIG. 2.—Case 1. R. C. X-ray of left knee, November 12, 1937, showing osteitis of lower end of femur healing with deformity of articular surface.

increasing swelling of the knee was noticed at one month of age. The child took its feeds well throughout. There was no gastro-intestinal disturbance and the child was not ill at any time. The child was sent to hospital when four and a half weeks old because of the swelling of the knee. At this time he was sturdy, vigorous, had a good colour and weighed 8 pounds 5 ounces. He was happy and free from pain unless the left leg was moved. There was a tense red swelling around the left knee-joint and a hard gland about the size of a walnut in the left groin. The left sternoclavicular joint also was swollen, red and tender. The child was admitted to hospital. Prontosil 2½ grains was given three-hourly for four doses without apparent effect. The knee joint was aspirated four times in the first ten days after admission, a total of 2½ ounces of pus being withdrawn. Staphylococcus aureus was isolated from the pus. After the last aspiration gentle extension was applied to the leg, and about ten days later the leg was put up in plaster of Paris with the knee extended as completely as possible—at about 160°. The sternoclavicular joint subsided without aspiration. While in hospital the child was apyrexial, apart from a rise of temperature between 99° F. and 101° F. for three days during the first

week. There was no fresh manifestation of sepsis except for a few pus cells in the urine on one occasion. The stools were usually normal, but occasionally relaxed. The child took its feeds well throughout, and his general condition never caused any anxiety. He was discharged at the age of seven and a half weeks weighing 9 pound 6 ounces. X-ray examination (Dr. Whately Davidson) two weeks after the onset of the swelling showed periosteal thickening of the distal half of the left femur and rarefaction and excavation of the distal end. A week later the condition had improved and fresh calcification had occurred at the distal end. Five weeks after the onset healing was advanced (see fig. 1 and 2). The condition was shown radiologically to be healed three months after the onset, but there was residual deformity and widening of the femoral epiphysis, and this has persisted. At the age of one year nine months the child's general condition was excellent, but there was considerable valgus deformity of the left knee joint which necessitated an iron support to the limb.

BLOOD COUNTS.—On admission, October 12, 1937, at one month of age : haemoglobin 75 per cent. ; white blood cells 23,000 per c.mm. ; polymorphs 67 per cent.

October 27, 1937 : haemoglobin 55 per cent. ; white blood cells 17,000.

November 11, 1937 : haemoglobin 70 per cent.

December 30, 1937 : haemoglobin 90 per cent. ; white blood cells 13,000 ; polymorphs 39 per cent.

Case 2. M. A. : This was a female child born at term on December 28, 1938, in a maternity hospital. Birth weight was 6 pounds 2 ounces. The mother had albuminuria during pregnancy, but the delivery and puerperium were normal and the child was not known to have had any contact with infection. The child was breast fed for ten days and then weaned. The first abnormal signs were swellings of both parotid glands and the right thumb at two weeks. A week later a swelling appeared over the right sternoclavicular joint. A few days later there was a purulent discharge from the left ear. The child was not ill at any time and there was no gastro-intestinal disturbance. She was admitted

FIG. 3.—Case 2. M. A. X-ray right hand, February 14, 1939, showing osteitis of first metacarpal and proximal phalanx with erosion of bones.

FIG. 4.—Case 2. M. A. X-ray right hand, March 21, 1939, showing healing osteitis with shortening and displacement of bones.

to hospital at one month of age. Her general condition was quite good and she weighed 6 pounds 10 ounces. She was happy and vigorous and took her feeds well. There was a fluctuating swelling over each parotid gland. The mouth and throat appeared clean and healthy. Red fluctuating swellings were present over the right sternoclavicular joints and the right first metacarpal bone. Four days after admission a swelling appeared around the right knee and a day or two later a tender red fluctuating swelling developed in the left hip region. The swelling at the base of the right thumb was incised and the swellings over the sternoclavicular and left hip joints were aspirated, the latter repeatedly. Staphylococcus aureus was isolated in pure culture from the sternoclavicular and left hip joints and from the discharge from the left ear. Three weeks after admission there was oedema of the labia and a vaginal swab gave a growth of staphylococcus aureus and b. coli. The parotid swellings subsided rapidly and the aural discharge cleared up in about six weeks. The temperature ranged between 98° and 100·2° F. during the first four weeks after admission and then fell to normal. The stools were relaxed during the first three weeks. The child's appetite was good throughout and her condition was never serious. X-ray examination (Dr. Whately Davidson) showed osteitis with considerable thickening in the lower end of the right femur and the upper end of the left femur, and osteitis of the adjacent ends of the first right metacarpal bone and proximal phalanx with considerable erosion of the joint surfaces (see figs. 3, 4, 5 and 6). Healing occurred rapidly in both femora without deformity. The child was discharged at the age of ten weeks weighing 8 pounds 2 ounces. When seen at the age of six months her general condition was excellent and no deformity could be detected except for shortening of the right thumb. The movements of the thumb were full and free.

FIG. 5.—Case 2. M. A. X-ray right knee, January 27, 1939, showing marked periosteal thickening over lower end of femur.

BLOOD COUNTS, February 13, 1939 (at the age of six weeks) : haemoglobin 58 per cent. ; red blood cells 2·8 millions per c.mm. ; colour index 1·03 ; white blood cells 22,500 per c.mm. ; polymorphs 33 per cent.

March 21, 1939 : haemoglobin 66 per cent. ; red blood cells 4·14 millions per c.mm. ; colour index 0·8 ; white blood cells 9,900 per c.mm.

April 18, 1939 : haemoglobin 62 per cent. ; red blood cells 4·2 millions per c.mm. ; colour index 0·74 ; white blood cells 9,000 per c.mm.

Case 3. Baby B. : This child was seen privately by Dr. A. G. Ogilvie, who has kindly supplied the notes. It was a female child born three weeks prematurely. Birth weight was 5½ pounds. Delivery and puerperium were normal. The child was breast fed, but there was difficulty with the feeding, possibly owing to prematurity. The child thrived fairly well. The cord did not separate until three weeks after birth, and left the umbilicus moist. At two weeks the left foot became puffy, but this subsided in a few days. At three weeks a swelling appeared over the left sternoclavicular joint. During the fourth week the legs became swollen, and the right knee and right shoulder

became red and swollen. When seen at one month of age the child was thin and looked like a premature child, but was fairly vigorous and had a strong cry. She was hungry for feeds and had no gastro-intestinal disturbance. The umbilicus had a small slough in one corner with some moistness around it. There was gross oedema of both legs involving the labia. The right knee, shoulder and sternoclavicular joints were swollen, red and fluctuating. The sternoclavicular joint was aspirated and thick pus which yielded staphylococcus aureus on culture was obtained. M and B 693, $\frac{1}{4}$ tablet, was given four times a day without apparent effect. During the next two months several fresh joints were affected and aspirated, but no incisions were made. The child recovered.

FIG. 6.—Case 2. M. A. X-ray of both femora and knee joints, March 21, 1939, showing healing of both femora with marked periosteal thickening, but no apparent deformity of the bones at the left hip or right knee joints.

Discussion

The cases here reported not only support the statements of Green and Dilliehunt that osteomyelitis of the long bones in infants is locally relatively benign, but also show that in uncomplicated staphylococcal osteomyelitis in the newly born there is practically no systemic disturbance. In these cases the mothers sought advice because of the swellings and not because the children

seemed ill. The infants slept and behaved normally and appeared to have no pain unless the affected bones or joints were moved. They took their feeds well throughout, and although there were occasional loose stools there were no serious gastro-intestinal disturbances. The pyrexia was slight in view of the suppuration and the conservative treatment adopted. Neither of the infants seen at the Babies' Hospital lost weight or appeared wasted at any time during the illness. Both gained eight ounces during the first month of life and about one pound during the second month. The first child, R. C., did not thrive normally between the second and sixth months and had recurrent attacks of gastro-enteritis, but after the sixth month he thrived steadily. The second child, M. A., has gained weight steadily since one month of age. There was moderate anaemia at about two months of age in each case. This improved as soon as the signs of active sepsis had cleared, but the child, M. A., developed hypochromic anaemia later. It is not clear from the reported cases if the prognosis is equally good in osteomyelitis in the newborn due to organisms other than the staphylococcus, but it is clear that if in a purely staphylococcal infection there is no infection of the lungs, peritoneum, meninges or skin, the prognosis, apart from the risk of deformity, is good. The parotitis and otitis present in the case M. A. did not apparently affect the prognosis adversely. There is evidently no urgency for operative treatment on account of either the local or the general condition. When the epiphyseal line is intracapsular there is a marked tendency to early infection of the joints because of the rapid escape of the pus through the cortex, but surprisingly little deformity or disability follows this joint infection. The only permanent deformities in the cases R. C. and M. A. have been due to erosion and shortening of the articular ends of the bones, and not to adhesions in the joints. These deformities occurred in one case following incision of the abscess and in one case following repeated aspiration. The advantage of repeated aspiration of the pus rather than open drainage is the avoidance of the risk of secondary infection of the wound, which was apparently the cause of death in one of the cases reported by Dunham.

Summary

Three cases of staphylococcus aureus infection of the long bones in the newborn are reported and discussed. The condition is found to be compatible with good general condition and good ultimate prognosis, apart from the risk of deformity, if the infection is unmixed and the lungs, skin, peritoneum and meninges are not involved. Repeated aspiration without open drainage gave good results and the lesions healed rapidly without sequestrum formation.

Thanks are due to Dr. J. C. Spence for suggesting this report and for valuable criticism, to Dr. Elsie Wright and Dr. Alan Ogilvie for permission to report their cases and to Dr. Norton, at the City Hospital for Infectious Diseases, Walker Gate, for the bacteriological work.

REFERENCES

Dilliehunt, R. B. (1935). *Surg. Gynec. Obstet.*, **61**, 96.
Dunham, E. C. (1933). *Amer. J. Dis. Child.*, **45**, 229.
Green, W. T. (1935). *J. Amer. med. Ass.*, **105**, 1835.
Mount, W. B. (1935). *Amer. J. Obstet. Gynec.*, **29**, 126.

CASE REPORT

HEPATOSPLENOMEGALY RESEMBLING NIEMANN-PICK'S DISEASE: RECOVERY FOLLOWING LIVER THERAPY

BY

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The following case is of considerable interest, as the patient showed many of the characteristics of Niemann-Pick's disease, yet recovery followed treatment with injections of liver extract.

Case report

D. N., a girl aged twelve months, was admitted on September 12, 1938. Nine months previously she was said to have had measles, and shortly after this the mother noticed that the abdomen was swollen. It had been gradually increasing in size since then. She had attacks of vomiting about every two weeks ; the appetite was poor ; the bowels were rather loose, with green frothy stools. The child became progressively paler and the general condition steadily deteriorated. There was no cough nor urinary symptoms.

FAMILY HISTORY.—The patient is the only child of healthy, unrelated parents, neither of whom is Jewish.

PREVIOUS HISTORY.—The labour was normal ; birth weight seven pounds. Breast fed for three months, then fed on milk, water and sugar mixture. First tooth appeared at seven months, but only two teeth were present at the time of admission. The patient had made no attempt to stand (fig. 1).

Condition on admission. A pale, rather sallow, puffy infant, with a markedly mongoloid appearance. Weight 17 pounds 10 ounces. Anterior fontanelle widely open.

ALIMENTARY SYSTEM. Tongue clean ; only two teeth present. Fauces healthy. The abdomen grossly distended, with an umbilical hernia. The liver is enlarged four fingerbreadths below the costal margin. The spleen is enlarged and extends two fingerbreadths below the costal margin. Both organs are smooth and firm.

CIRCULATORY SYSTEM. Pulse is regular, rate 130 per minute. The heart apex is in the fifth space and not displaced. The heart sounds are normal.

RESPIRATORY SYSTEM showed no abnormality.

CENTRAL NERVOUS SYSTEM. No abnormality detected apart from great muscular hypotonia. Fundi oculorum normal.

FAECAL FAT. Total 20 per cent. of dried faeces ; split 16 per cent., unsplit 4 per cent.

URINE contains no abnormal ingredients.

X-RAY of the bones of the forearm and skull shows no abnormality.

BLOOD. Haemoglobin 66 per cent. ; red blood cells 5,252,000 per c.mm. ;

colour index 0·8 ; white blood cells 22,500 per c.mm. ; polymorphs 46 per cent., lymphocytes 48 per cent., mononuclears 4 per cent., eosinophils 1 per cent., basophils 1 per cent.

MANTOUX REACTION (1 in 10,000) negative.

WASSERMANN REACTION negative.

BLOOD CHOLESTEROL. 533 mgm. per 100 c.c. serum. The serum is milky in appearance.

BLOOD SUGAR CURVE. Percentage at half-hourly intervals after ingestion

FIG. 1.—Before treatment. Liver and spleen outlined.

of 7 grammes of glucose : 0·095 (fasting)—0·109—0·113—0·100—0·90. No glycosuria.

PROGRESS. The liver and spleen increased steadily in size, and the condition of the patient rapidly deteriorated. The weight had fallen to 16 pounds by November 7, 1938.

The case was diagnosed as Niemann-Pick's disease. The only alternative appeared to be an infantile form of Gaucher's disease. Moncrieff (1930) has summarized the difference between these diseases, and in view of the sallow skin, the mongoloid appearance, the absence of leucopenia and particularly the raised blood cholesterol in the present patient, the above diagnosis was made. The only sign of Niemann-Pick's disease absent was enlargement of the lymphatic glands.

Splenic puncture was performed. The films showed reticulo-endothelial cells in a vacuolated matrix. At first it was thought that some of the cells

themselves showed vacuoles. The films were submitted to several pathologists, who were unable to give any definite opinion. Eventually they were sent to Dr. G. W. Nicholson, who reported as follows :—' The film . . . does not justify dogmatic statements. The vacuoles appear to me to be all intercellular, i.e. artefacts, and I can see nothing resembling foam cells.'

The case appeared to be hopeless, but at the time there was a patient suffering from coeliac disease in the ward who was responding remarkably well to treatment by injections of crude liver extract. It occurred to one of us (J. H. D. M.) that as he also had a high blood cholesterol, the patient under discussion might also benefit from this treatment. Accordingly on November 11, liver therapy was started. 2 c.c. of campolon were injected on alternate days for three weeks. From November 30, 1938, until January 29, 1939, injections were given twice weekly, and from that date until the time of writing 2 c.c. have been given at weekly intervals.

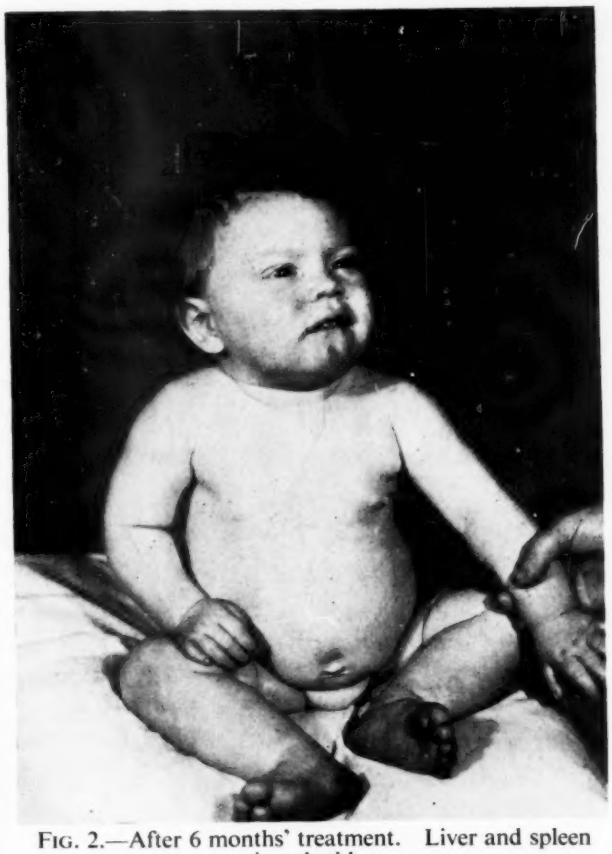

FIG. 2.—After 6 months' treatment. Liver and spleen impalpable.

A fortnight after the treatment had begun the liver and spleen had decreased considerably in size. There was a striking change in the patient ; she became alert and playful, and her facial appearance returned to that of a normal child. She lost her fretfulness, began to speak and attempted to walk (fig. 2).

BLOOD CHOLESTEROL : 336 mgm. per cent.

BLOOD COUNT. Red cells 5,749,000 per c.mm. ; haemoglobin 97 per cent. ; colour index 0·85 ; white cells 27,812 per c.mm. ; polymorphs 30 per cent., lymphocytes 62 per cent., mononuclears 4 per cent., eosinophils 4 per cent.

BLOOD SUGAR CURVE was unchanged.

The improvement was steadily maintained. By January 21, 1939, the abdomen had returned to normal proportions, neither liver nor spleen being palpable. The weight had risen to 19 pounds, although there was a slight initial loss.

BLOOD CHOLESTEROL : 168 mgm. per cent.

By February 27 the weight was 20 pounds 8 ounces, the patient took a lively interest in her surroundings, walked, and talked. Mentally she was quite up to the standard for her age. The liver and spleen were still impalpable.

BLOOD CHOLESTEROL 180 mgm. per cent.

When last seen on April 11, 1939, the weight was 21 pounds 4 ounces, and the child seemed quite normal in every way (fig. 3).

Discussion

The disease from which this patient suffered is evidently some form of lipoidosis, which does not conform to any of the described types. In view of Dr. Nicholson's report on the slides from splenic puncture the diagnosis of Niemann-Pick's disease cannot be maintained, although clinically the patient presented a typical picture of this disease. The successful result of liver therapy, moreover, does not correspond with the invariably fatal outcome of this malady. In a valuable paper on the subject Atkinson (1937) collected

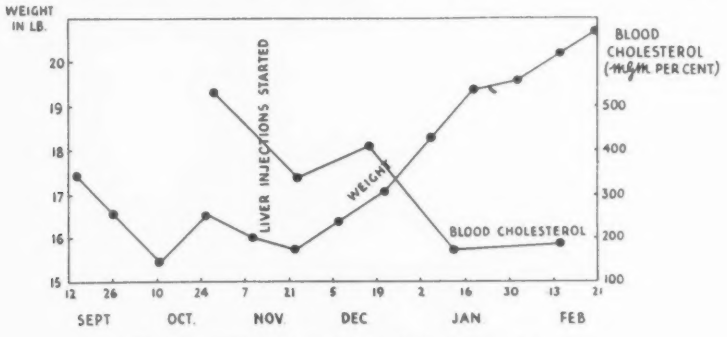

FIG. 3.—Weight and blood cholesterol curves.

forty-two cases from the literature up to 1936. Of these three were alive at the time of their being reported, their ages being seventeen, nine and a half and seventeen and a half months respectively. They were all gravely ill, and had shown no sign of improvement during the course of the illness. Of the other thirty-nine, only four lived into the third year. Since Atkinson's paper, Freudenberg (1937) has reported a case of twins with Niemann-Pick's disease, one of whom survived to the thirty-first month, and Müller (1938) has recorded a case which lived for twenty-five months.

The fact remains, however, that a gravely ill infant, with great enlargement of the liver and spleen and with lipaemia, recovered dramatically after receiving injections of liver extract. It remains to be seen if other lipoidoses will not respond in a similar manner, and this case suggests a possible line of treatment for a group of diseases the majority of which end fatally.

REFERENCES

Atkinson, F. R. B. (1937). *Brit. J. Child. Dis.*, **34**, 245.
Freudenberg, E. (1937). *Z. Kinderheilk.*, **59**, 313.
Moncrieff, A. (1930). *Arch. Dis. Childh.*, **5**, 265.
Müller, H. (1938). *Z. Kinderheilk.*, **59**, 476.

INTERNATIONAL CONGRESS OF PEDIATRICS

The American officers of the International Congress have decided that the international situation is such at the present time that it seems advisable to postpone to an indefinite date the Fifth International Congress of Pediatrics which was scheduled to be held in Boston, Massachusetts, U.S.A., September 3, 4 and 5, 1940.

A SYNDROME CHARACTERIZED BY ECTODERMAL DYSPLASIA, POLYDACTYLY, CHONDRO-DYSPLASIA AND CONGENITAL MORBUS CORDIS

REPORT OF THREE CASES

BY

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The association of the four following congenital abnormalities—ectodermal dysplasia affecting the hair, teeth and nails ; polydactyly ; chondro-dysplasia ; and congenital morbus cordis—has been observed in two children in whom the clinical picture is so strikingly similar as to justify its description as a separate syndrome. Although many atypical cases of achondroplasia and chondro-osteo-dystrophy have been recorded with associated abnormalities, and there is an extensive literature relating to congenital ectodermal dysplasia, we have found no detailed description of the syndrome previously published. McIntosh (1933), however, in the tenth edition of ' Diseases of Infancy and Childhood ' includes illustrations and some clinical particulars of a child who is clearly an incomplete example of the same syndrome. He has kindly furnished a full report on this case, and it is included as case 3 in the present series ; thanks are also due to Dr. S. Levine, Professor of Pediatrics at the New York Hospital, for permission to include subsequent observations made on the same patient.

In Cockayne's (1933) comprehensive review of the literature relating to inherited abnormalities of the skin, there are no examples showing more than two features of the tetrad. One such is that described by Windle (1891). In this instance, a female of a German family from Eisenbach, in whom deficiency of teeth with conical incisors was inherited as a simple dominant, married a man suffering from polydactyly, and had two children with both polydactyly and dental abnormalities. This family is of particular interest in showing how a possible linkage of characters may arise, but this will necessarily be of extreme rarity, since it will require the two characters to be in corresponding chromosomes, the linkage then only occurring by means of a cross-over. (In the present cases neither the dental defect nor the polydactyly was inherited as a mendelian dominant.) Pires de Lima (1923) also records dominant polydactyly and premature eruption of teeth (as seen in case 1 of the present series) occurring separately in several members of a family and united in one member.

There are numerous examples of polydactyly of recessive type being

associated with abnormalities of the skin and its appendages, such as ringed hair and melanodermia described by Meachen (Cockayne, 1933), albinism (Pearson et al., 1913), epidermolysis (Callomon, 1910), and dominant ichthyosis (Hofmann, 1927), but none of these show any close similarity to the present syndrome with the possible exception of Betz's case (Cockayne, 1933), in which recessive polydactyly was associated not only with an ectodermal defect (aplasia cutis congenita) but also with atresia of the pulmonary artery.

Although a variety of congenital abnormalities including hypospadias, spina bifida, defective auricles, cleft palate (Emerson, 1909), herniae, and congenital cystic disease of the kidneys (Porak and Durante, 1905), have been described in association with achondroplasia, there does not appear to be any recognized tendency for achondroplasiacs to suffer from either congenital morbus cordis, ectodermal defect, or polydactyly. The only suggestive case of which an account has been found is that of a 'polydactylous monster' found drowned in the river at Amsterdam and dissected by the anatomist Ruysch. The skeleton was described by Kerckring in his Spicilegium Anatomicum in 1670, and it is clear from the description and illustration of both the long bones and skull that the condition was in fact achondroplasia. The infant bore a total of thirty-one digits ('inaudita hactenus foecunditate'), seven on each hand, eight on the right foot and nine on the left. Unfortunately there is no record of either the nails or the heart, but it is tempting to speculate whether it was entirely coincidence that this child should have been described in the same city as that in which case 2 of the present series was observed many generations later.

The following three cases are therefore presented as examples of a hitherto unclassified syndrome. The name 'chondro-ectodermal dysplasia' is tentatively suggested, as emphasizing the association of two outstanding features. (The term 'chondro-dysplasia' rather than 'achondroplasia' has been used in describing the osseous condition in these patients, since it differs in certain respects, which will be discussed below, from the classical picture of achondroplasia.)

Case reports

Case 1. M. C., a girl, aged 20 months, was referred to Guy's Hospital on May 17, 1939, by Dr. H. R. Kidner. She is thought to have been four or more weeks premature, weighing $4\frac{3}{4}$ lb. (2·200 kgm.) at birth. Pregnancy and delivery were uneventful. At birth, it was noted that the nails were defective and that two upper incisor teeth were present. (One of these latter subsequently fell out spontaneously and the other was removed.) The infant sucked, breathed, and cried normally, and had not appeared cyanotic or dyspnoeic at any time. She was fed on dried milk, with the addition of orange juice and cod-liver oil after the age of three months. She had been well throughout infancy, and had gained weight steadily.

The mother and father are both healthy, but are first cousins, the father's mother and mother's mother being sisters. It was only possible to examine the mother, who is normal, but she is well acquainted with a large proportion of her own and her husband's nearer relatives, and knows of no other example of micromelia or ectodermal defect in either family.

Physical examination (May 17, 1939.) A well-nourished infant, weighing 24 lb. (11·64 kgm.). The mentality is normal for age. She is of good colour, with no cyanosis or clubbing. Height 74·5 cm.

ECTODERMAL DEFECTS.—The nails of both hands and feet show an extreme

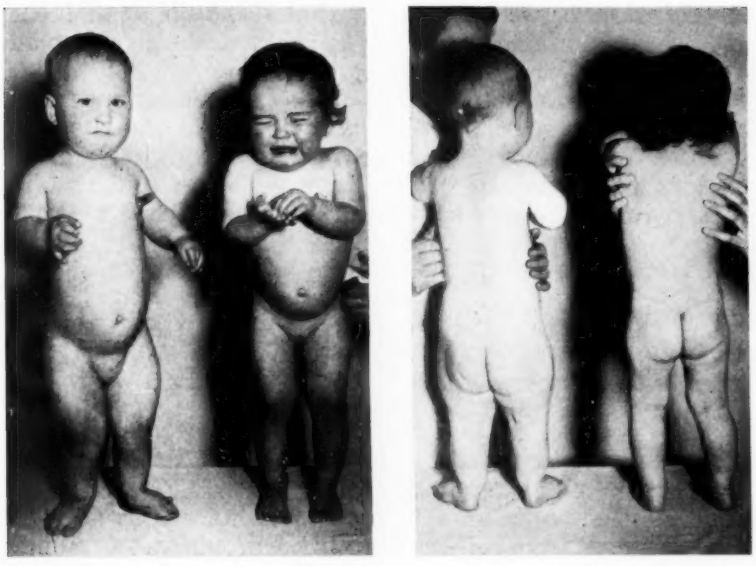

FIG. 1 (a and b).—Front and back view of case 1, aged 20 months, with normal control of same age, showing short limbs, long trunk and paucity of hair.

degree of dysplasia, and are altogether absent from the thumb, index, and sixth fingers of both hands.

The hair is fine, fair, and sparse. (Microscopical examination of a hair showed no abnormality.) The scalp is dry and scaly, but the skin elsewhere appears normal.

FIG. 2.—Hands (case 1). Polydactyly and dystrophy of nails.

REPORT ON DENTAL CONDITION (Mr. R. E. Rix) :

UPPER JAW. The only teeth erupted are the first and second deciduous molars. They are slightly more conical in shape than are commonly seen. The usual bulbous sides of the teeth are flattened from the cervical margin to the occlusion surface. The cusps and ridges are accentuated and the fissures deep, thus giving a crenated appearance to the occlusal surface.

There are localized swellings of the gum in the region of the deciduous central incisors suggestive of their imminent eruption.

There is no sulcus between the gum pad and the lip. The labial mucous membrane is attached along the ridge in the deciduous incisor and canine regions.

LOWER JAW. The only teeth erupted are the first deciduous molars. They present the same characteristics as the upper molars.

The general level of the gum pad is interrupted by a depression on each side of the deciduous lateral incisor region. From the centre of the gum pad lying between these two depressions a fraenum labii is attached which bifurcates as it passes forward to fuse with the lip.

RADIOLOGICAL EXAMINATION OF JAWS :

Deciduous teeth present but unerupted — $\frac{C\ A}{E\ C} \mid \frac{A\ C}{C\ E}$

Permanent teeth in process of calcification — $\frac{6}{6} \mid \frac{6}{6}$

There is no evidence of any other teeth.

In spite of the absence of teeth the jaws are not small, and the antero-posterior relationship of the jaws to each other is normal.

The SKULL and face appear clinically and radiologically normal, and do not show the characters typically seen in achondroplasia. Circumference of head 44·7 cm. Intermeatal measure (over vertex) 30·7 cm. External occipital protuberance to nasion (over vertex) 29 cm.

LIMBS AND TRUNK. The limbs are extremely short in relation to the long trunk, and have the proportions of those of an achondroplasiac, the proximal segments being more reduced than the distal. Owing to the great length of the trunk, however, there is no dwarfing. There are six digits on each hand and five on each foot. The sixth finger (which is situated on the ulnar side of the hand) is well formed and is partially but not completely mobile, interfering to a slight extent with manual dexterity.

RADIOLOGICAL EXAMINATION of the long bones show the short, thick bones of achondroplasia with a tendency to exostosis in the region of the hips.

FIG. 3.—Femora (case 1), resembling achondroplasia, with tendency to exostosis in region of hips.

FIG. 4.—Left leg (case 1).

FIG. 5.—Right arm (case 1).

The terminal phalanges of the fingers are poorly developed. A sixth metacarpal bone is present on the left, and there is partial division of the fifth metacarpal on the right. The spine shows no abnormality.

MEASUREMENTS :

Trunk length (seventh cervical to tip of coccyx) 37 cm. (i.e. half the total height).

Circumference of chest (nipple level) 46·5 cm.

Upper extremity :

Acromion to olecranon process 11·5 cm.

Acromion to radial styloid 18·5 cm.

Lower extremity :

Anterior superior iliac spine to mid-patella 16·5 cm.

Anterior superior iliac spine to internal malleolus 28 cm.

Circumference of abdomen (umbilical level) 48·5 cm.

HEART. The area of cardiac dullness extends from one fingerbreadth to the right of the sternum, to the nipple line in the fifth left intercostal space. The rate is 100 to 120 per minute. A loud rough systolic murmur is best heard over the third and fourth intercostal spaces to the left of the sternum, but is conducted over the precordium.

ORTHODIAGRAM : heart : M.T.D. 8·2 cm. Chest : 12·2 cm.

ELECTROCARDIOGRAM normal.

FIG. 6.—Skiagram of heart (case 1), showing enlargement.

OTHER EXAMINATIONS. The lungs, abdomen, central nervous system, special senses and genitalia were normal. The Wassermann reaction was negative. The urine showed a slight trace of albumin in one specimen only but no other abnormality.

Case 2. M. D., a boy aged 4 years 3 months, was admitted to the Paediatric Clinic of the University of Amsterdam on April 5, 1939. He was born spontaneously at full term in January 1935, weighing 5½ lb. (2·5 kgm.). A second child, also a boy, born subsequently, is quite normal. Pregnancy and delivery were uneventful. The child was breast-fed for three months, but growth was impaired from birth. The first teeth appeared after the age of two years, and were of peculiar shape (see below). In 1937 a sixth digit was removed from the ulnar side of both hands. The child contracted whooping cough in 1937

and measles in 1938. The appetite had always been poor, and there had been frequent abdominal complaints.

There is no consanguinity of the parents. The mother suffers from bronchial asthma. No deformities are known on either side the family.

Physical examination (April and June 1939).—The patient is a well-nourished boy weighing 12 kgm. The mentality is normal for age, the child having a great capacity for clowning. The colour is good and there is no cyanosis or clubbing.

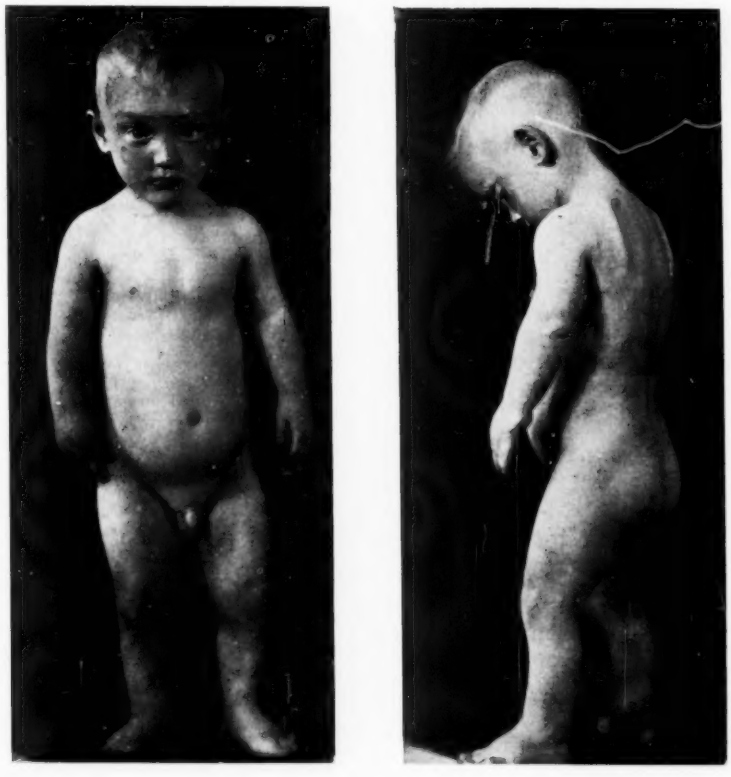

FIG. 7 (a and b).—Front and side view of case 2, showing short limbs, long trunk, facies and paucity of hair.

There is abundant perspiration on the head. Numerous small lymph-glands are palpable in the neck and groins.

ECTODERMAL DEFECTS. The nails of all the fingers and toes are small and dystrophic, resembling small scales. The hair of the head is fair, fine and scanty, especially in the temporal and occipital regions, and the eyebrows are scanty. Microscopical examination of a hair showed no abnormality. The scalp is somewhat dry, but the skin elsewhere is normal with the exception of some eczematous patches on the face.

REPORT ON DENTAL CONDITION (Mr. W. L. van Andel) :

UPPER JAW. On either side, two hypoplastic deciduous molars are present. In addition, there are two conical-shaped canines. One central deciduous incisor has erupted, and one central deciduous incisor is unerupted. The lateral incisors are absent.

LOWER JAW. On either side, two hypoplastic deciduous molars have erupted. There are in addition two conical-shaped canines and two central deciduous incisors, the latter being bell-shaped. The lateral incisors are absent.

FIG. 8.—Hands (case 2). Dystrophy of nails.

The impression is obtained that the frenulum is as wide as the four deciduous incisors ; on lifting the upper lip, the labial mucous membrane is seen passing over without interruption into the mucous membrane of the palate, the central incisor perforating this membrane.

RADIOLOGICAL EXAMINATION OF JAWS. No permanent incisors are visible in either jaw, but only the first molars ; in the lower jaw, only the first premolars and possibly a permanent cuspid can be seen.

SKULL. The skull is clinically and radiologically somewhat enlarged, and the forehead prominent. Clinically, the fontanelle appears closed. The face is small with a pointed chin, and slightly sunken nasal bridge. Radiologically, the anterior fontanelle is still visible and the frontal suture patent. The sella turcica is normal. Changes typical of achondroplasia are absent.

Circumference of head 49·2 cm. ; intermeatal measure (over vertex) 32 cm. ; external occipital protuberance to nasion (over vertex) 31·5 cm.

FIG. 9.—Left leg (case 2). Short thick tibia ; lines of arrested growth at lower end of femur.

LIMBS AND TRUNK. The limbs are short in relation to the long trunk, and the proportions are those of an achondroplasiac. On the ulnar sides of both hands a scar shows the site of removal of a sixth digit. There are five digits on both feet. The hands are small and plump, with short and shapeless fingers. The index fingers deviate to the radial side, and the little fingers are slightly curved. The lower limbs are also short and plump, with short digits.

RADIOLOGICAL EXAMINATION. The long bones are short and thick, but do not otherwise show the typical structure of achondroplasic bones. Several lines of arrested growth are visible. The proximal tibial epiphysis on either side is poorly developed. The metatarsal and metacarpal bones are

FIG. 10.—Feet (case 2). Thick metatarsals. Dystrophy of terminal phalanges.

more typical of achondroplasia. The terminal phalanges of the fingers and toes are poorly developed. The bones of the wrist show partial synostosis ; their number corresponds to the age of the patient. A sixth metacarpal is visible on the left.

MEASUREMENTS :

Height 81 cm. Trunk length (seventh cervical vertebra to tip of coccyx) 40·5 cm. (i.e. half of the total length). Circumference of chest (nipple level) 48 cm. Circumference of abdomen (umbilical level) 48·2 cm.

Upper extremity :

Acromion to olecranon process (left and right) 14 cm.
Acromion to radial styloid 18 cm.

Lower extremity :

Anterior superior iliac spine to mid-patella (left and right) 19·5 cm.
Anterior superior iliac spine to internal malleolus 31 cm.

HEART. The area of cardiac dullness extends from one fingerbreadth to the right of the sternum to the left nipple line in the fifth intercostal space. A loud rough systolic murmur is best heard over the apex. The heart rate is 80 to 110 per minute.

ORTHODIAGRAM. Heart : M.T.D. 10 cm. Chest : 14·6 cm.

ELECTROCARDIOGRAM normal.

LIVER AND SPLEEN palpable 1½ fingerbreadths below the costal margin.

GENITALIA. Penis small ; testicles undescended.

OTHER EXAMINATIONS. Lungs, central nervous system, and special senses normal. The Wassermann reaction was negative, the tuberculin test negative and the urine and stools normal.

FIG. 11.—Skiagram of heart (case 2), showing enlargement.

BLOOD. No anaemia. Differential blood count normal. Inorganic phosphate 4·4 mgm. per cent. Phosphatase 6·8 units. Serum calcium 11 mgm. per cent.

Case 3. Bernice P. was admitted to Babies Hospital, New York, January 19, 1932, at the age of 4 years 4 months. The complaints were : retarded physical growth, supernumerary digits, and squint.

The father was 29 years of age, living and well, and the mother 27 years of age, living and well. (It was later learned that the father and mother are first cousins.) Both parents are of Jewish stock. There had been two pregnancies : 1, the patient, and 2, a miscarriage, induced, at three months' gestation.

There was no family history of tuberculosis, syphilis, or of any congenital malformations.

The patient was born at term by difficult breech delivery ; weight at birth, 7 lb. 2 oz. (3·235 kgm.). No difficulty in resuscitation.

She was breast fed for three months. Cereals and soup were begun at five months. The rest of her feeding history is not remarkable. Her appetite was never very good, but she had no digestive disturbances and showed no food idiosyncrasies.

She sat up alone at five months ; walked at nine months. First tooth erupted at fourteen months, an upper incisor. For the first year and a half she is said to have gained weight steadily, but at that time it was noticed that her height was small for her age. At two years of age she was 28 inches (71·2 cm.) tall. (She did not attend school until seven years of age, but since that time she has always kept up well with her coevals and has constantly been in the ' honour group.')

No illnesses of note.

Physical examination (January 1932, aged 4 years 4 months). Weight, 13·60 kgm. Height, 84 cm. (33 ins.). Head to umbilicus, 41 cm. ; umbilicus to sole, 45 cm. Circumference of head, 47·5 cm. A well-nourished but short

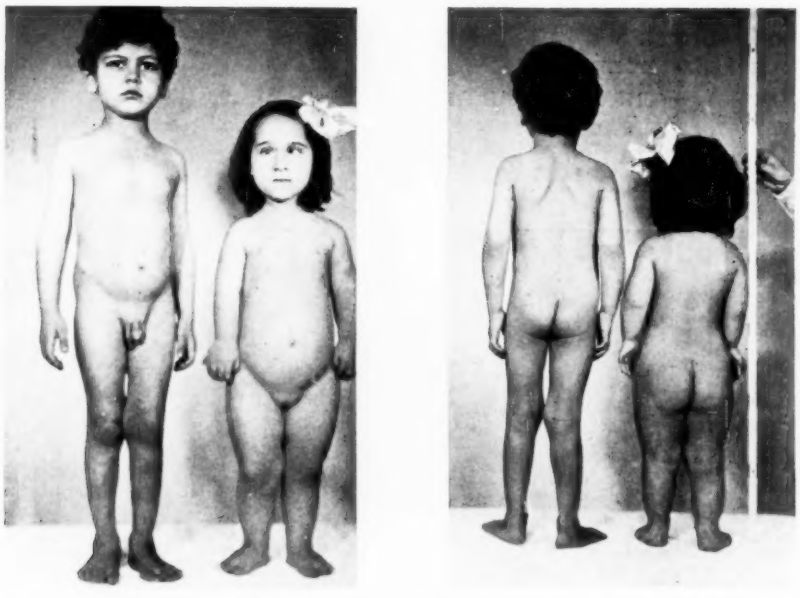

FIG. 12 (a and b).—Front and back view of case 3, aged 4 years 4 months, with normal control of same age. Note short limbs, trunk of normal length, facies.

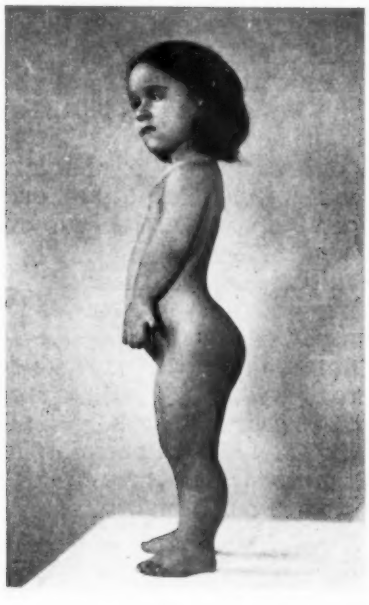

FIG. 13.—Lateral view of case 3 showing prominent frontal region and lordosis.

and abnormally developed girl. All four extremities relatively short. Six fingers on each hand.

Skin normal. Nails hypoplastic (see below).

No lymph-gland enlargement.

Prominent frontal and parietal bossing of skull, symmetrical.

Fixation with right eye. Internal squint of left eye of about 20 degrees of arc. Spasm of left inferior oblique muscle. Conjunctivae, sclerae, pupils and eyegrounds normal.

Ears and nose normal.

REPORT BY DENTAL CONSULTANT. 'This child's teeth are very rudimentary in form. The superior and inferior deciduous lateral incisors are missing. Dental films show congenital lack of the developing tooth buds of the superior and inferior central and lateral incisors. Calcification of the

FIG. 14.—Teeth of case 3 (aged 4⅓ years), showing location and conical incisors.

deciduous teeth seems to be complete. Resorption does not appear to have begun. The developing buds of the rest of the permanent teeth are present and development would seem to be normal for a child of this age. There is some dental caries present. Both right and left lateral roentgenograms show evidence of calcification in the submaxillary glands.'

No other abnormality of buccal cavity or pharynx. Tonsils present.

Thyroid isthmus palpable ; enlargement questionable.

Thorax poorly developed but symmetrical. No evidence of abnormality in heart or lungs. Blood pressure 105/85.

Abdomen soft, tympanitic, slightly distended. Liver edge just palpable below costal margin. Spleen not palpable.

Conspicuous shortening of all four extremities. The extra digit on each hand is adjacent to the little finger ; it is incapable of independent motion. The hands and feet are broad and stubby. There is marked lumbar lordosis.

BLOOD. Haemoglobin, 14·3 grammes per 100 c.c. ; red blood cells, 5·0 million per c.mm. ; white blood cells, 13,300 ; polymorphonuclears, 74 per cent. ; lymphocytes, 24 per cent. ; monocytes, 1 per cent. ; eosinophils, 1 per cent. Red cells and platelets appear to be normal.

URINE. Alkaline ; specific gravity, 1020 ; albumin, 0 ; reduction 0 ; acetone, 0 ; occasional single leukocyte and a few epithelial cells.

TUBERCULIN TEST (Mantoux, 0·1 mgm.), negative.

BLOOD CHEMISTRY. Blood non-protein nitrogen, 35 mgm. per 100 c.c. ; sugar, 95 mgm. per 100 c.c. Serum calcium, 11·6 mgm. per 100 c.c.; inorganic phosphate (as phosphorus), 4·1 mgm. per 100 c.c.; cholesterol, 211 mgm. per 100 c.c. Plasma albumin, 5·1 grammes per 100 c.c.; fibrinogen, 0·26 grammes

per 100 c.c. ; carbon dioxide combining power, 36·4 volumes per 100 c.c. Kahn test negative.

BASAL METABOLIC RATE, 41·6 calories per sq.m. per hour. Total calories, 23·7 per hour. On account of the abnormal proportions in this child's height measurements, the basal metabolism was calculated by two different standards. Using height and weight according to Dubois, the result is 21·7 per cent. below normal. However, when weight alone is used (Dryer), the result is +0·7 per cent. In this situation, the latter figure is probably the more reliable, since the patient presumably has an unusual surface area as regards her chronological age.

RADIOLOGICAL REPORT. There are extensive multiple abnormalities in the long bones. The metacarpals and phalanges are short. Both hands show six fingers, with fusion of the fifth and sixth metacarpals on the left. The carpal centres are small on both sides and consist of one unusually large bone in the centre of the carpus, with three small centres visible on the left, and one on the right.

The radii and ulnae are short and of bizarre shape. The cortices are not thickened, and bear a practically normal relationship to the medullary cavities. Bone trabeculation does not appear to be definitely altered. The distal ends of the bones have a ragged limiting boundary, but provisional zones of calcification are intact and in no way resemble rickets. The humeri show shallow bowing, with convexity directed posteriorly.

FIG. 15.—Right arm of case 3 (aged 4⅓ years). Short radius and ulna of abnormal shape ; shallow bowing of humerus.

In the feet the proximal phalanges are visible in all five toes on each side. In the fifth toe on each side, only the proximal phalanx shows calcification. The same is true of the fourth toe on the right, but a small centre of ossification can be seen on the left representing the middle phalanx. In the third toe the middle phalanx shows some calcification on each side. In the second toe three phalanges can be seen on each side, though the distal phalanx is rudimentary. (The terminal phalanges of the fingers are also small throughout, and the distal phalanges of the fifth and sixth digits show no calcification.) The metatarsals are short and thick. Centres for the semilunar, scaphoid and cuboid bones are visible in each tarsus.

The tibiae and fibulae are both short and heavy. The distal ossification centre of the fibula is unusually large on each side, and there is marked roughening and irregular condensation of bone at the distal ends of both tibiae and in the distal tibial centre of ossification. There is apparently a fusion of the ends of the shaft of the fibulae with the distal ossification centre of both tibiae. At the proximal end of the left tibia, a small exostosis projects downward and medially from the medial aspect of the metaphysis. The proximal ends of the

tibiae are greatly widened and show a small, irregular centre of ossification situated medially. In contrast to this, the distal ends of the femora are approximately normal in the antero-posterior view, with very little deformity of the centres of ossification. There is moderate coxa vara with no dislocation of the hips.

In the lateral view of the skull the clinoid processes are large. The bones seem to be of normal density. There is a moderate increase in the digital markings, but not enough to warrant an interpretation of increased intracranial pressure. At the same time, the suture lines are unusually small for a child of four years, the coronal suture being practically closed. Following the horizontal ramus of the mandible, from the angle through two-thirds of the posterior portion, there is a strip of abnormal density parallel to the bone and situated about 1 mm. away in the soft tissues. This strip consists of multiple small shadows of calcium density, clustered in three main groups. The interpretation of these shadows is uncertain.

This is an interesting combination of bone and cartilage dystrophy, which, while resembling achondroplasia, has many additional changes which hardly

FIG. 16.—Legs (case 3). Short and heavy tibiae, with irregular condensation of bone at distal ends ; exostosis at proximal end of left tibia.

admit such a simple classification. The changes all represent abnormalities of bone growth, with tendency to shortening of all the long bones, and perhaps fusion of the carpal bones, together with spur formation on the left tibia and marked irregularity of the growing ends of the bones throughout. The changes at the distal ends of the tibiae are interesting and difficult to interpret. A descriptive classification of these changes would include chondrodystrophy, polydactylism, and solitary exostosis of the left tibia.

NOTE BY DR. A. A. WEECH (February 3, 1932). 'This child presents a combination of two forms of congenital anomaly, the first affecting skeletal growth and producing the approximate picture of chondrodystrophy, the other affecting several of the tissues of ectodermal origin. The child, though four years old, measures only 33 inches in height, and the central point of the body lies about one-half inch above the navel. The hands hanging at the sides extend approximately as far as the greater trochanter of the femur. The shortening

of the extremities is especially noticeable in the fingers. In addition to the supernumerary digits, which have already been described, one finds an apparent ankylosis of the index fingers of both hands. The nails of both fingers and toes are extraordinarily hypoplastic. They show in general a tendency to convexity in form and are more thickened at the tip than at the base. Several of the nails

FIG. 17.—Hands (case 3). Polydactyly and dystrophy of nails.

stand out at an angle from the nail bed. The supernumerary digits show no nails. Examination of the other ectodermal tissues discloses a rather fine head of hair with apparently normal eyebrows and eyelashes ; these parts cannot be considered abnormal. The teeth disclose cone-shaped upper and lower

FIG. 18.—Feet (case 3). Dystrophy of nails.

central incisors with absence of the lateral incisors, but aside from caries the teeth in the rear of the mouth are normal. There is no noticeable abnormality of the skin itself ; that is, there are no papular lesions on the face, the vermilion border of the lips is well defined, the sweat and sebaceous glands are both apparently functioning normally, and both mammary glands are normally

developed. There is nothing abnormal in the configuration of the ears, and the conformation of the head is not unusual. The patient presents a left internal strabismus.

'The patient's ectodermal anomalies are interesting in that no hereditary factors have been uncovered, and in the nature of the abnormalities of the teeth and nails. The type of teeth are those which occur in the anidrotic type of ectodermal dysplasia, a group of cases in which the hereditary transmission is sex-linked in character, whereas the nails are similar to those which occur in so-called combined dystrophy of the hair and nails (Clouston, 1929 ; Jacobsen, 1928), a group in which the transmission is mendelian non-sex-linked in type. The presence of factors from both groups tends to show the impossibility of a sharp clinical differentiation of such anomalies into rigid categories.'

PROGRESS. The parents have steadily refused to submit the child to operative correction of strabismus or resection of the supernumerary digits. The tonsils and adenoids were removed in October 1937. Apart from measles at five years of age, complicated by otitis media (left), and chickenpox at nine years of age, there have been no important illnesses.

In May, 1938, when the patient was 10½ years of age, she was studied at New York Hospital. Weight, 23·4 kgm. Height, 114 cm. Circumference of head, 52 cm. She was of normal intelligence. Most of the physical findings are comparable to those given above, but there are additional details in regard to the extremities. Both arms and legs are much shorter than normal and have a contracted, truncated appearance. The soft tissues appear abnormally bulky for the length of the members. Motility of the muscle groups is impaired. Both hands are broad and pudgy, with stubby fingers. There is only one functioning phalangeal joint in each finger, except in the index fingers, both of which are stiff. The supernumerary fingers appear to function as well as the others. In the feet, which are also stubby, the first and third toes on each side override the second toe, which appears shorter than the rest. The nails on all fingers and toes are distorted, tiny brownish structures which project slightly upward. The laboratory tests reported are essentially normal, except that the basal metabolic rate is calculated to be +35 per cent. X-ray examination shows six metacarpals on the right, and an attempt to form six on the left, but the two lateral ones are fused. There is also fusion of the capitate and hamate on both sides. Two of the metacarpals on the right show double epiphyses. The femora are shortened and thickened, with irregular epiphyseal lines and spur formation. No permanent tooth buds are seen in the lower incisor region. The fourth and fifth metatarsal bones on the left are fused proximally, and similar but less marked fusion is seen on the right.

In view of the occurrence of congenital morbus cordis in cases 1 and 2, the patient was re-examined at the New York Hospital in November 1939, at the age of twelve years one month.

The HEART showed no enlargement to percussion, the rhythm was regular, and the sounds of good quality. In the supine position only there was a faint systolic murmur, heard just to the left of the sternum. The murmur was inconstant and disappeared entirely when the patient sat up. The blood-pressure was 120/90, and the pulse rate 98.

RADIOLOGICAL REPORT. Film and fluoroscopy of the chest show a symmetrical thorax. The diaphragms are smooth and the angles are clear. The heart is normal in size. There is some fullness of the pulmonary conus. There are no abnormalities of the bony cage.

Analysis of the syndrome

Osseous system. In all three cases, the long bones are short and thick, the radiological changes corresponding more or less closely to the classical

picture of achondroplasia, though the additional changes seen in case 3 make some qualification of the diagnosis necessary. As is usual in this condition, the proximal segments of the limbs tend to be more reduced in length than the distal. Case 1 shows a tendency to exostosis in the region of the hips. Case 3 shows spur formation on the left tibia and irregular condensation at the distal ends of both tibiae, with fusion of the shaft of the fibula with the distal centre of ossification of the tibia on both sides, whilst the distal ends of the radii and ulnae have a ragged limiting boundary. Parsons (1936) has expressed the

FIG. 19.—Skiagram of hands (case 1). Sixth metacarpal present on right ; fifth left metacarpal partially divided. Dystrophy of terminal phalanges.

FIG. 20.—Skiagram of hands (case 2). Partial synostosis of carpal bones. Sixth metacarpal present on left. Dystrophy of terminal phalanges.

FIG. 21.—Skiagram of hands (case 3, aged 4 years 4 months). Single large carpal bone in centre of carpus. Sixth metacarpal present in right ; fusion of fifth and sixth metacarpals on left. Dystrophy of terminal phalanges.

view that typical achondroplasia should be regarded as only one manifestation of chondrodystrophy (or more correctly, chondrodysplasia) of which hereditary deforming chondrodystrophy, Ollier's disease, and Morquio's disease are further examples. Instances such as case 3, which show features of more than one type of chondrodystrophy, would appear to substantiate this view.

The skull in case 1 does not show the brachycephaly and hydrocephalic appearance commonly (but not invariably) seen in achondroplasia due to premature fusion of the base, and the radiological appearance and facies are normal. Cases 2 and 3, however, do show some enlargement of the skull and

depression of the nasal bridge, although the skiagrams are not altogether typical of achondroplasia.

The trunk in the first two cases appears exceptionally long, not only in relation to the short legs but (in case 1) in comparison with a normal control. In both cases, there is little or no lordosis and, at their present ages, practically no dwarfing. The length of the trunk (seventh cervical vertebra to tip of coccyx) is in both instances almost exactly half the standing height. In case 3, on the other hand, both lordosis and dwarfing are well marked.

Polydactyly. This is remarkably similar in each case, a sixth digit being present on the ulnar side of each hand and the feet being unaffected. In case 2 the extra digits have been removed, but in cases 1 and 3 they form functional fingers with a moderate degree of movement, though giving rise to some clumsiness ; both these cases show radiologically a separate sixth metacarpal on the left and a partial division of the fifth metacarpal on the right (fig. 19, 20 and 21). In case 2 there is the remainder of a separate sixth metacarpal on the left and a wide fifth metacarpal on the right. In each case the terminal phalanges are poorly developed and calcified, and there is a tendency to fusion of the carpal bones.

Ectodermal defects. In all three cases the nails and teeth were affected, and in cases 1 and 2 the hair was abnormally sparse, although showing no microscopic abnormality. The sweat glands appeared to function normally in each case, nor was there chronic rhinitis as is frequently seen in the anidrotic type of ectodermal dysplasia.

Weech (above), who examined case 3 in 1932, considered that the abnormality of the teeth corresponded most nearly to that seen in the anidrotic type of ectodermal dysplasia. This latter condition occurs either as a sex-linked recessive, or an incomplete dominant (Cockayne, 1933), ' sparing the females or affecting them as a rule less severely.'

The defect of the nails closely resembles that described by Clouston (1929) and others, Weech's observation (above) being borne out by the fact that cases 1 and 2 show in addition hypotrichosis (' hypotrichosis et dystrophia unguium '), although in none are the defects associated with pigmentation or any evidence of hypothyroidism. Cockayne (1933) shows that the existing figures bear out the assumption that hypotrichosis et dystrophia unguium is a dominant, whilst the great majority of the recorded cases have been of French or French-Canadian origin, if not actually related. In none of the present series, however, is there evidence of French descent or dominance.

The three cases here described appear therefore to belong to a type of ectodermal dysplasia which does not correspond exactly with any one recognized form, either clinically or genetically (see below).

Congenital morbus cordis. In cases 1 and 2, the orthodiagram shows gross cardiac enlargement, particularly to the right, the M.T.D. being 8·2 cm. (chest 12·2 cm.) and 10 cm. (chest 14·6 cm.) respectively. A loud systolic murmur was present in both cases, best heard in case 1 in the third and fourth intercostal space to the left of the sternum, and in case 2 at the apex. In neither case was cyanosis or clubbing observed, and there was no dyspnoea. A patency

of the septum ventriculorum might account for the signs in both cases, though it would be unusual to get such degree of cardiac enlargement without any cardiac symptoms.

The third case was investigated both clinically and radiologically and no evidence of congenital morbus cordis found, if the transient and positional systolic murmur heard to the left of the sternum be disregarded.

Physical development. Two out of the three children were small at birth, case 1 weighing 4¾ lb. (2·2 kgm.) and case 2 weighing 5½ lb. (2·5 kgm.). Case 3 was of normal weight (7 lb. 3 oz.). Apart from their deformities, all three children are now robust and in good general health.

Race. The three children are of English, Dutch and Jewish American extraction respectively.

Discussion

The most significant points in the family histories of these three cases are that in two out of three instances the parents were first cousins, and in no case were any of the features of the syndrome known to have existed in relatives. The latter observation is the more likely to be reliable since, with the exception of congenital morbus cordis, any one of the components (ectodermal defects, chondro-dysplasia, and polydactyly) would almost certainly have excited comment in the family. It is therefore strongly suggested that the syndrome had been inherited as a recessive gene or genes and had appeared, apparently de novo, on the union of two individuals both carrying the recessive character.

It is impossible at present, in view of the small number of cases observed, to do more than speculate as to the mechanism of appearance of such a bizarre collection of abnormalities. As indicated above, the ectodermal dysplasia must be considered as distinct both from the anidrotic type which occurs as a sex-linked recessive or incomplete dominant, and from hypotrichosis et dystrophia unguium, which occurs as a dominant. Polydactyly may occur as either dominant or recessive, but true achondroplasia is probably an incomplete dominant (Cockayne, 1933), a further reason for describing the osseous condition in these cases not as classical achondroplasia but as 'chondro-dysplasia.' Possibly a linkage of recessive genes such as that postulated in relation to the Laurence-Moon-Biedl syndrome (Cockayne et al., 1935; Sorsby et al., 1939) would account both for the variety of the structures involved and for the extreme rarity of the syndrome. If such were the case, one might expect to find one or more components of the syndrome appearing separately in collaterals.

In addition to the Laurence-Moon-Biedl syndrome, and those examples of ectodermal defect linked with abnormalities of the mesoderm mentioned above, conditions which excite comparison are arachnodactyly, in which the bony abnormalities are frequently associated with congenital morbus cordis and dislocation of the lens; cleido-cranial dysostosis, with associated defects of the teeth (La Chapelle, 1919); and gargoylism (Ellis et al., 1936), in which condition chondro-osteo-dystrophy is linked with a number of more or less

constant abnormalities including congenital opacities of the cornea and hepato-splenomegaly. Each of these conditions therefore shows a combination of mesodermal and ectodermal defects, and it remains to be proved whether they are in fact the result of a linkage of genes, or whether a single gene may be responsible for the whole picture.

Summary

1. A syndrome consisting of ectodermal dysplasia affecting the hair, nails, and teeth ; polydactyly ; chondro-dysplasia, and congenital morbus cordis, is described. No detailed account of this syndrome has been found in the literature.

2. The full syndrome was observed in two children, and a third child showed all the components except hypotrichosis and congenital morbus cordis.

3. Two of the patients were females and one male. They were of English, Dutch and Jewish American race respectively.

4. In two out of the three cases, the parents were first cousins. No similar condition had been observed amongst relatives. The condition is held to be a mendelian recessive, without sex-linkage.

Thanks are due to Dr. Rustin McIntosh and Dr. S. Levine ; and to Dr. E. A. Cockayne for his helpful criticism.

References

Callomon (1910). *Arch. Derm. Syph., Wien*, **104**, 292.
Clouston, H. R. (1929). *Canad. med. Ass. J.*, **21**, 18.
Cockayne, E. A. (1933). *Inherited Abnormalities of the Skin and its Appendages*, London.
——, Krestin, D., and Sorsby, E. (1935). *Quart. J. Med.*, **4**, 93.
Ellis, R. W. B., Sheldon, W. P., and Capon, N. B. (1936). *Ibid.*, **5**, 119.
Emerson, C. P. (1909). *Achondroplasia*, Osler and Macrae's *Modern Medicine*, London, **6**, 683.
Hofmann, E. (1927). *Zbl. Haut-u. GeschlKr.*, **23**, 619.
Jacobsen, A. W. (1928). *J. Amer. med. Ass.*, **90**, 686.
Kerckring, T. (1670). *Spicilegium Anatomicum*, Amsterdam.
La Chapelle, E. H. (1918). Thesis, Leyden.
McIntosh, R. (1933). Holt and Howland, *Diseases of Infancy and Childhood*, tenth ed., New York, 362.
Parsons, L. G. (1936). *Achondroplasia, Brit. Encyclopaedia of Med. Practice*, **1**, 135. London.
Pearson, K., Nettleship, E., and Usher, C. H. (1913). *Drapers Co. Res. Mem.*, Biometric Ser. **9**, *Albinism in Man*, London.
Pires de Lima, J. A. (1923). *Bull. Soc. Anthrop. Paris*, **4**, 71.
Porak, C., and Durante, G. (1905). *Nouvelle Iconographie de la Salpétrière*, **17**, 481.
Sorsby, A., Avery, H., and Cockayne, E. A. (1939). *Quart. J. Med.*, **8**, 51.
Weech, A. A. (1929). *Amer. J. Dis. Child.*, **37**, 766.
Windle, B. C. A. (1891). *J. Linn. Soc.* (Zool.), **23**, 473.

THE CLINICAL PICTURE OF STAPHYLOCOCCAL INFECTIONS IN THE NEWBORN

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In recent years there has been increased interest in infective conditions among the newborn, and it has become evident that the conditions of institutions for the newborn are often such as to favour the occurrence and spread of infection. The staphylococcus is recognized as ubiquitous and a potentially pathogenic organism. Its constant presence in the air and on healthy hands (Devenish and Miles, 1939) and frequent presence even in the throats and milk of healthy mothers (Benians and Jones, 1929) have recently been demonstrated. This paper is an attempt to present the clinical features of the various types of disease which may occur in the newborn as a result of infection with this organism and the conditions under which such disease is liable to occur. As far as possible the material is drawn from cases personally observed at the Babies' Hospital or in the infant or maternity wards of the General Hospital, Newcastle-upon-Tyne, but the whole picture of staphylococcal infection in the newborn has necessarily been completed from published accounts of certain conditions by other authors.

Blepharitis, staphylococcal ophthalmia neonatorum, and umbilical infection

These are undoubtedly the most common forms of neonatal staphylococcal infection. They are usually mild and referred to as 'sticky eyes' or 'sticky umbilicus.' The eye infection is occasionally severe and accompanied by oedema of the eyelids and copious pus formation. When mild it usually clears within about ten days, but when severe may persist for several weeks, and in one case (R.P. see below) was followed for several months by recurrent discharge of pus from the lachrymal duct. Superficial pustules may develop on the cheek when the discharge is free, but this is commonly a surface infection only and not associated with the appearance of sepsis elsewhere. The umbilical discharge usually clears rapidly and persists only in the presence of a polyp. Infection of either the eyes or the umbilicus may be followed by signs of generalized sepsis and spread of the infection by the blood stream, of which the following case is an example.

* In receipt of a Medical Research Council Fellowship.

Case 1. R. P. The child was healthy at birth. A purulent discharge from the eyes at the age of three days was followed by a purulent umbilical discharge after the separation of the cord. The child failed to thrive. At two months of age pyuria developed, and was followed by acute spasmodic bronchitis and septic spots. Cough and wheezing became persistent, and there was recurrent purulent discharge from the left lachrymal duct. The gain in weight was slow, but the appetite was fairly good. From the age of six months there was irregular and unexplained pyrexia. At seven months several subcutaneous abscesses developed on the scalp and the child died apparently with an exacerbation of the chest condition. As is so often the case in infants with this type of disease post-mortem examination did not reveal any apparent naked-eye lesion in the lungs sufficient to account for death, or any localized pus.

This child evidently had an abnormally poor resistance to staphylococcal infection. Whilst the prognosis in any case of neonatal staphylococcal infection of the eyes or umbilicus is usually good, it should be remembered that a few infants have a poor resistance and the infection may be followed by a generalized spread. This will usually be made evident in a few weeks by either failure to gain weight or further signs of sepsis.

Perionychiae and septic spots

These are common forms of neonatal sepsis and were considered by Brewer (1937) to be 'part of the ordinary work of baby routine.' They are, however, definite evidence of infection among the babies and it was noticeable in the maternity ward that after several weeks of complete freedom from any infection among the mothers or babies there would be a period of a week or so in which several infants would have a few septic spots or perionychiae. These periods of infection often coincided with the development of head colds or mild sore throats among the mothers, but it was often not the child of the infected mother who developed the sign of infection, and it would appear that there existed at these times a high carrier rate among the occupants of the ward. Small perionychiae appeared to be of no significance. One infant had a severe septic thumb with swelling of the whole terminal phalanx and pus round the base of the nail, but there was no disturbance of general health or of weight gain, and no further sign of sepsis developed during the next ten weeks. It was thought that this was probably due to a high degree of immunity in the child and the rapid localization of the infection, and that the lesion was potentially dangerous. In 1925 Castle reported the case of an infant who developed a festered thumb at the age of nine days. This was followed by septic spots, otitis media, an abscess in the temporal region, and a series of subcutaneous abscesses. There was pyrexia but no disturbance of general health and the child ultimately recovered. Blood culture gave a pure growth of staphylococci on two occasions.

An attempt was made to determine on clinical grounds whether each type of septic spot was of grave or little significance. When the small and completely superficial pustule was the only evidence of sepsis, it was not followed by any other sign of sepsis. In two cases isolated flaccid bullae which contained frank pus showed no tendency to spread and on desquamation left dry skin which rapidly healed. They appeared to be purely superficial and of much less grave import than the dome-shaped bulla with clear straw coloured contents

which appears in pemphigus. When multiple and confluent, however, these flat bullae with purulent contents may be followed by deeper septic lesions, although the bullae themselves heal rapidly. As opposed to these lesions the septic spot which is really a subcutaneous abscess, and the diffuse dull red papular or petechial rash of generalized sepsis are of grave significance, because they denote a blood stream infection. Some infants escape further evidence of infection as did the child with the severe septic thumb, but a subcutaneous abscess in the newborn is a potentially dangerous lesion.

Case 2. K. H. The child was healthy at birth. At the age of eight days it developed a septic spot on the scalp. For a month fresh spots appeared almost daily, and although most were superficial a few were described as being like small abscesses. At five weeks both ears began to discharge. When seen at the age of two months the left ear was discharging profusely and the pus yielded numerous colonies of staphylococcus aureus and several colonies of haemolytic streptococci. A post-auricular abscess and a small abscess on the cheek were both present and due to staphylococcus aureus infection. The general condition was fairly good and improved steadily.

The following case illustrates the significance of a generalized papular or petechial rash in the newborn.

Case 3. J. P. The child was healthy at birth. There was mild blepharitis with a little purulent discharge for a few days after birth. At ten days the child developed a generalized dull red papular and petechial rash. The mouth and tongue were inflamed and dry, and the motions were green and choppy. The temperature was between 98·2° F. and 101° F., but there was no obvious septic lesion until a week later when a small subcutaneous abscess (staphylococcus aureus) developed in the thigh. The temperature fell to normal, the rash faded and the abscess was aspirated but the child lost weight steadily and was very ill. At the age of five weeks she was small and wizened. The skin was dry and loose and the deep subcutaneous fat had been lost. She was taking her feeds fairly well, and there was no vomiting, diarrhoea or sign of local sepsis. During the next week a small abscess developed in the left axilla and at the same time the general condition improved. A diffuse papular rash appeared several times during the next few months, but her general condition improved steadily, there was no further pus formation and at five and a half months she weighed sixteen pounds.

Pemphigus neonatorum, exfoliative dermatitis neonatorum and Ritter's disease

Many cases and outbreaks of skin lesions in the newborn have been described in the past few years under the above headings. Ritter described the condition which bears his name as non-contagious, but as it was endemic in the institution in which he observed it and he personally observed 297 cases (Guy and Cohen, 1929) this was probably not the case, and it is now generally agreed that the three conditions are probably due to the same infection. Staphylococcus aureus has been the causative organism in all the outbreaks recently described, but an isolated case reported by Guy and Cohen was attributed to b.pyocyaneus infection. The essentials of the recently reported outbreaks are as follows.

Most institutional outbreaks occurred either in the presence of a skin lesion in one of the mothers or staff (Falls, 1917 ; McCandlish, 1925 ; Benians and

Jones, 1929) or when the institution was overcrowded and understaffed (Brewer, 1937). In some cases the outbreaks were mild and easily controlled (Brewer, Benians and Jones), in one case it was prolonged for eight months in spite of vigorous efforts to stop it, and Falls reported an outbreak in which healthy mothers carried the infection from the infected institution to infants over two years of age in another institution. In all outbreaks the lesions both in adults and in the infants were vesicular rather than follicular, and in the infants were followed by desquamation. In severe cases desquamation was preceded only by redness of the skin without vesicle formation and large areas of corium were exposed, the whole lesion resembling a burn. The desquamation was followed by rapid healing. Constitutional symptoms were usually absent even in the presence of extensive desquamation, but a few infants died apparently of exhaustion. Seeds (1929) reported a case in which miliary staphylococcal abscesses of the lung followed pemphigus neonatorum.

The following is an almost identical case.

Case 4. P. D. The infant was born healthy. At three weeks a red patch appeared on one cheek. Two days later a similar patch appeared on the other cheek. On the following day red patches appeared on the legs ; the child was fretful and developed a slight cough. There was a purulent discharge from the eyes. On the fifth day large bullae developed on the hands and feet and several smaller vesicles in the groins and on the thighs and buttocks. Desquamation occurred around the anus and the external genitalia. The cry was hoarse, there was a loose cough with upper respiratory embarrassment, and a few coarse râles were heard over the bases of the lungs. On the following day desquamation was beginning over the red indurated areas, there were several fresh bullae, and the original ones had increased in size. The gums and buccal mucosa were intensely inflamed and ulcerated and feeding was extremely difficult. Fluid from an unruptured bulla yielded staphylococcus aureus in pure culture. Death occurred on the following day, seven days after the first sign of redness on the cheeks. At post-mortem examination (Dr. G. Davison) there was no abnormality of the internal organs except for the lungs which were studded with small whitish areas rather larger than pinheads and indistinguishable by the naked eye from miliary tubercles. Histological report on a portion of the lung : 'Miliary focal necrosis and abscess. Abundant masses of organisms, which are obviously etiologically related to the condition and not post-mortem growth. Organisms are cocci and more like staphylococci than streptococci. The condition, at least in the terminal stage, would seem to have been pyaemic.'

The next case, in which death was due to exhaustion and toxaemia, shows how easily pyaemia may occur when the infant is infected shortly after birth.

Case 5. A. E. Child was healthy at birth. On the third day a small blister appeared in the right groin. This burst overnight and left a raw area on the thigh. The following day a small blister appeared on the cheek, and on the fifth day after birth a similar one developed on the hand. Meanwhile the child was taking its feeds well and seemed to gain weight. There was a little regurgitation of food but no vomiting or diarrhoea. On the seventh day extensive desquamation occurred and the skin lay in loose shreds. The lips were excoriated and the mouth sore. The eyelids were slightly swollen and there was some mucopurulent discharge. There was a little moistness at the attachment of the umbilical cord. The child died on the following day. A swab taken from beneath loose skin immediately after death yielded b.coli and staphylococcus albus, and a swab taken from around the umbilical cord at the same time yielded a heavy growth of staphylococcus albus. At post-

mortem examination no significant abnormality of any organ was observed. Portions of lung, liver, spleen, kidneys and suprarenal were examined histologically with negative results. The following was the report on the umbilical cord, umbilicus, and vessels : ' A large abscess impinging on and actually entering a blood vessel which looks more like the umbilical artery than an umbilical vein. Masses of organisms are present in the pus and appear by oil immersion lens examination to be staphylococci and not streptococci.'

The following cases are interesting because they are consecutive children of the same parents, both cases of intra-uterine infection, and they illustrate the two extremes of the course of the disease.

Case 6. S. T. Normal pregnancy, delivery and puerperium. Birth weight seven pounds. Child was plump, vigorous and well developed at birth, but there was an area of desquamation on the left thigh and haemorrhagic blisters were present on the fingers. When admitted to hospital twelve hours after birth the whole of the skin was bright red, there were areas of desquamation on the thigh, fingers, chest and several dome-shaped bullae with clear serous or blood-stained fluid were present on the hands. On the following day the bullae contained haemorrhagic, purulent fluid which contained many diplococci. On culture staphylococcus albus and aureus were obtained. During the first month fresh superficial bullae with clear contents developed daily and were followed by desquamation. Large areas of desquamation appeared also without previous bulla formation and exposed freely bleeding corium which in some places discharged pus on the surface. Healing occurred rapidly from the edges of the desquamated areas. The child's weight remained stationary at about six pounds twelve ounces, and the child was vigorous and took its feeds well. The temperature ranged between 98° F. and 100° F. There was no cough or pyuria. At five weeks of age the temperature was between 100° F. and 102° F. for two days. During the next week the child lost six ounces and the motions became relaxed but not frequent, and there was a slight cough. From this time the bulla formation and desquamation became less extensive. At eight weeks of age pitting oedema developed in the legs and back, followed by oedema of the face and ascites. The weight rose to seven pounds three ounces. At this time a small subcutaneous abscess developed on the arm. The oedema passed off and the weight fell to six pounds twelve ounces. The child remained vigorous and had a good appetite. She was at this time ten weeks old and had presumably grown in spite of the persistent sepsis, because, although still the same weight as at birth, she was losing subcutaneous fat, her face was pinched and her body and limbs were small. At twelve weeks an abscess developed on her head. From this time she began to lose ground, although the weight remained stationary until about a week before death. The appetite became poor, all the subcutaneous fat was lost and the child became less vigorous. The temperature ranged between 98° F. and 100·6° F. A few fresh bullae and subcutaneous abscesses developed. During the last few days before death the temperature rose to 104° F. Death occurred at the age of seventeen weeks. On post-mortem examination, apart from the skin lesions and total absence of fat, no abnormality was discovered.

Case 7. E. T. Sister of case 6, was born fifteen months later, after normal pregnancy, delivery and puerperium. The child was well nourished and vigorous at birth but the whole of the intact skin was bright red. Large areas of desquamation were present, the skin lying in loose shreds and exposing the corium. The lips were excoriated. The child was admitted to hospital four hours after birth. The temperature was normal. Further desquamation occurred and the child rapidly lost strength. Death occurred on the third day

after birth after a rise of temperature to 103° F. Post-mortem examination was not allowed.

The above cases were nursed under barrier conditions and no spread of the infection occurred.

Staphylococcal osteomyelitis

This is an unusual but not rare form of neonatal sepsis. Both Green (1935) and Dilliehunt (1935), when discussing osteomyelitis in infancy, quoted cases which occurred in the neonatal period. They stressed the fact that the condition is locally relatively benign and that relatively conservative treatment suffices. In two cases seen at the Babies' Hospital in the last two years the same features were noticeable and the lesions subsided with surprisingly little or no deformity after repeated aspiration of the pus. The clinical features in these cases were strikingly different from those observed in older children in that there was practically no systemic disturbance. The mothers noticed swellings over the bones and joints of their apparently healthy infants and sought advice. In both cases the pus had ruptured into the joint when the child was first seen.

Although several bones were affected, the course of the disease was practically apyrexial, there was no loss of weight or reason for anxiety in the general condition and the lesions healed rapidly. The cases were fully reported with x-ray plates in this journal (Cass, 1940).

Staphylococcal pneumonia

Aerogenous staphylococcal pneumonia among the newborn is an interesting though rarely recognized condition.

Smith (1935) described an outbreak of four cases in a maternity hospital. There had been several cases of breast abscess among the mothers and septic spots among the babies in the three weeks immediately preceding the outbreak. During and immediately after the outbreak eleven infants were isolated on account of mild catarrh of the upper respiratory passages, and nasal and throat swabs from these and from apparently healthy infants who were not in isolation gave a high proportion of profuse growths of staphylococcus aureus, indicating a widespread staphylococcus aureus carrier condition among the infants. Among ten fatal cases of staphylococcal pneumonia reported by Macgregor (1936), one was in a premature child sixteen days old. In all the cases the clinical picture is striking. An apparently healthy infant suddenly becomes dyspnoeic and feverish. Blood stained fluid is coughed up, vomited, or discharged from the nose. Signs of pneumonia develop and the child dies between eighteen and forty-eight hours after the first sign of illness. The post-mortem findings are equally characteristic. Blood-stained serous fluid is present in one pleural sac, subpericardial haemorrhages or bloodstained fluid in the pericardial sac, and either a portion or the whole of one lobe is sharply defined, haemorrhagic and consolidated. The remaining lung tissue appears healthy. Blood may be present in the gastrointestinal tract. Histological examination of the affected lung tissue reveals consolidation with much haemorrhage and exudate and large clumps of staphylococci. Abscess formation is evidently extremely rapid and was starting in a case reported by Smith (1935) in which death occurred thirteen hours after the onset of symptoms.

There is no clear description of a case of staphylococcal pneumonia in the newborn followed by recovery. Kanof et al. (1939) reported twelve cases of primary and eleven of secondary or pyaemic staphylococcal pneumonia, of

which nine and five respectively occurred under one year of age. No neonatal cases are specifically mentioned and a clinical picture of the disease at this age is not given, but the clinical picture of the cases as a whole was similar to that of pneumococcal pneumonia except for the early and frequent occurrence of empyema in the staphylococcal cases. The mortality under one year of age, was 75 per cent. in the primary and 100 per cent. in the secondary cases. Macgregor (1936) describes similar cases in young infants, but all were fatal.

The following case was recently seen in this hospital.

Case 8. L. B., aged ten weeks, weighing 8 lb. 14 oz., was stated to have been pale and thin from birth. Pyuria and infantile eczema were present. Ten days after admission the temperature rose to between 101° F. and 103° F. and the child developed a cough and signs of bronchitis. Five days later 40 c.c. of pus containing staphylococcus aureus were aspirated from the left pleural cavity. In the following six weeks 361 c.c. were aspirated, the temperature gradually fell, and the child made a complete recovery.

Had the lung lesion not been followed by an empyema in this case, it would not have been diagnosed as staphylococcal pneumonia. It is possible that staphylococcal pneumonia can be a relatively mild condition in the newborn and is then unrecognized.

Staphylococcal meningitis

This appears to be a rare condition in the newborn. Craig (1936) reported twenty-one cases of neonatal meningitis. Of these, three were due to a pure staphylococcus aureus infection and three to staphylococcus aureus in combination with b.coli or streptococci. All the cases were fatal. Fifteen of the twenty-one infants were premature and although there is no note of the length of gestation in the staphylococcal cases it is clear that feeble and premature infants are particularly liable to develop meningitis in the presence of sepsis. The diagnosis of meningitis in the newborn is evidently difficult and in only four cases was it made before death. The most constant clinical features were poor appetite, increasing weakness and stationary or falling weight. Hippocratic facies, signs of cerebral irritation such as mental restlessness, darting movements of the tongue, nystagmus, unequal pupils and exaggerated reflexes developed later in some cases and suggested the need for a lumbar puncture, without which the diagnosis could not be made. Localized or general convulsions occurred in ten cases ; neck rigidity and Brudzinski's sign in only two cases. Sponginess of the fontanelle was present in nine cases. Vomiting was unusual and not projectile. Fever was usual but not constant. The pulse was in most cases rapid and almost imperceptible. In the three pure staphylococcal infections death occurred fifteen, ten and seven days after birth. In one a dorsal meningo-myelocele was present and the condition was diagnosed during life. In one there was purulent conjunctivitis with corneal ulceration, and staphylococcus aureus was isolated from the eye discharge during life. In the third case an extensive pustular skin eruption and pneumonia were present before death and at autopsy staphylococcal lung abscesses were found.

Bloch and Pacella (1938) reported a case of staphylococcal meningitis in a seventeen-day-old infant successfully treated with sulphanilamide.

The child had an occipital meningocele removed at the age of six days. The post-operative course was uneventful, but at the age of sixteen days the infant became fretful and refused its feeds. Three generalized convulsions occurred. When seen thirty-six hours later, the temperature was normal and there were no abnormal neurological signs. A swelling was present under the operation scar and when the scab was removed a thick layer of pus containing many staphylococci was exposed. The cerebrospinal fluid was under slightly increased pressure and was cloudy. Intrathecal and oral sulphanilamide were given, the temperature subsided on the ninth day, the cerebrospinal fluid became sterile on the eleventh day, the superficial infection of the meningocele subsided and recovery occurred without complications.

This case differs from those reported by Craig in that the meninges were infected by local spread rather than by the blood stream, and circumstances suggested the diagnosis in the early stages of the disease before neurological signs had developed and the cerebrospinal fluid became purulent.

It appears that in any premature and feeble infant, or one with a congenital abnormality of the meninges, in whom there is evidence of staphylococcal infection elsewhere, weakness, loss of weight and refusal of feeds (which as already stated above, is an unusual symptom in staphylococcal infection even when severe and accompanied by a fall in weight) should suggest meningitis. Lumbar puncture in the early stages may lead to an early diagnosis and successful treatment. Evidence of cerebral irritation may develop later but the classical signs of meningitis are usually absent throughout the disease.

Staphylococcal septicaemia

In recent years there have been many reports of neonatal staphylococcal septicaemia. It is evident that many of the conditions described above are actually manifestations of septicaemia and the clinical diagnosis can be made without bacteriological confirmation. It is interesting, however, to review the clinical conditions in which the bacteriological diagnosis has been made.

Castle reported a case, already mentioned, of multiple subcutaneous abscesses in which two positive blood cultures were obtained. In 1933 Dunham reported eleven cases of staphylococcal septicaemia in which the diagnosis was made on positive blood cultures. Three recovered and eight died. The commonest clinical feature was pyrexia at some stage of the disease, present in ten cases. Jaundice, together with an enlarged spleen, fever and haematuria, was the presenting symptom in three cases. In two of these no frank sepsis manifested itself throughout the illness. In three others there was an indefinite clinical picture of pallor, cyanosis, fever and dehydration without frank sepsis. In these five cases fever was the only definite evidence of infection and the diagnosis of septicaemia could not be made on clinical grounds alone. In all the other cases there was clinical evidence of blood stream infection such as a petechial rash, otitis media, multiple abscesses, osteomyelitis or meningitis. Mount (1935) reported a case of staphylococcal septicaemia with positive blood culture. Low fever, a deep abscess in the arm with pus in the elbow joint, and abdominal distension were the chief clinical features. In contrast to these cases in which a positive blood culture has confirmed the clinical diagnosis or provided a diagnosis when the clinical signs were indefinite, is the case reported by Seeds and quoted above, in which in spite of pemphigus neonatorum and a high temperature a blood culture was negative on the fourth day. Death

occurred on the tenth day and multiple pyaemic abscesses in the lungs were found at autopsy.

In the light of these cases there seems to be no reason why the diagnosis of septicaemia should be limited to those cases in which it is proved bacteriologically. A petechial rash, multiple subcutaneous abscesses, any deep-seated lesion such as a deep abscess, osteomyelitis or meningitis is equally good evidence of spread by the blood stream. The adult picture of septicaemia with rigors, high fever and sweats is never seen in the newborn, but rapid loss of weight and wasting are the equivalent signs of septicaemia as opposed to bacteraemia.

Staphylococcal gastro-enteritis

There have been many reported attacks of staphylococcal food poisoning in adults during the past few years. In some it has been proved without reasonable doubt that the staphylococcus isolated from the food was responsible for the illness by the production of a similar illness in human volunteers after the ingestion of the organism or a filtrate prepared from its culture (Denison, 1936 ; Kelly and Dack, 1936). No cases occurring in infancy have been reported, but Blackman (1935) reported a fatal case in a twelve-year-old child.

The onset was sudden with vomiting, headache and fever about five hours after the last ingestion of food. The vomiting continued, diarrhoea began about eighteen hours after the onset, and the child became unconscious six hours later. On admission to hospital thirty-six hours after the onset she was comatose. The temperature was 103·4° F., pulse rate 130, and the respirations were rapid, deep and laboured. Haemolytic staphylococcus albus was isolated from the blood and the condition was evidently one of septicaemia rather than a purely gastro-intestinal infection at this time. That the original infection had been by the intestinal tract was, however, proved by post-mortem examination ; this revealed intense inflammation and ulceration of the jejunum and ileum, and the presence of greyish red fluid and moulds of mucosa of jejunum and ileum with fibrino-purulent exudate, pus cells and clumps of staphylococci in the lumen of the bowel. The colon was normal apart from haemorrhages into the mucosa. The other findings were those of staphylococcal septicaemia.

This picture differs from that of staphylococcal septicaemia of parenteral origin as it occurred in the Bundaberg fatalities in that the gastro-intestinal symptoms are more severe and persistent and gross changes in the gastro-intestinal tract are found at post-mortem examination.

It is probable that only certain strains of staphylococci produce enterotoxin and that certain conditions of growth are necessary for its production (Dolman, 1934). This may explain the apparent infrequency of staphylococcal gastro-enteritis. There seems to be no doubt that the injection of staphylococcus enterotoxin causes gastro-enteritis in susceptible children and adults. Whether or not the conditions under which the food of the newborn is prepared are ever suitable for the production of enterotoxin if the necessary strain of staphylococcus is present, and whether or not the newly born are susceptible to this toxin when ingested, are not known. By analogy an outbreak of such an infection would be expected to be explosive and limited to those infants who had partaken of the food containing the toxin. Also by analogy the illness

should be severe and short, with vomiting, diarrhoea and toxaemia, and marked signs of enteritis should be found at post-mortem examination in fatal cases. In all reported cases staphylococci have been isolated from the food or from the post-mortem lesions. As Topley and Wilson (1936) pointed out, the staphylococcus is such a common organism that one cannot incriminate staphylococci isolated from the suspected food without first proving that they are capable of producing enterotoxin under the conditions under which the food was prepared.

It may be that with increasing awareness of the possibility of staphylococcal gastro-enteritis paediatricians may be able to diagnose the condition if it occurs in the newly born and in time define the clinical picture.

Anaemia as a sign of neonatal infection

In staphylococcal neonatal infection anaemia develops slowly and is rarely, if ever, the most striking feature of the case. In purely superficial infection it was not observed. In all the infants with signs of blood stream infection the haemoglobin fell to between 50 per cent. and 66 per cent. between the sixth and twelfth week of life, but at this stage of the disease the obvious manifestations of sepsis were still present and were more striking than the pallor. The anaemia was more severe in the cases which presented the clinical picture of septicaemia than in those of bacteraemia. In both it was orthochromic and developed slowly from birth in spite of adequate doses of ferrous, copper and manganese sulphate. When the infection had become localized and was beginning to clear up, the blood returned to normal. In one case in which iron was not administered at this stage, hypochromic anaemia developed during convalescence from the infection. In case 6, S. T., in whom the infection was never completely localized and death eventually occurred, the haemoglobin remained at 50 per cent. from the age of nine weeks until just before death at the age of seventeen weeks. It appears that in blood stream staphylococcal infection in the newborn moderate or severe anaemia usually develops slowly and cannot be prevented by the administration of iron, but when the infection has been overcome the blood will return to normal if the supply of iron is adequate. When there is failure completely to localize and overcome the infection, anaemia persists in spite of iron therapy, and it is probable that unrecognized and unlocalized infection may explain the condition of some infants under six months of age with persistent anaemia which resists treatment.

Discussion

Benians and Jones (1929) demonstrated that of healthy mothers in the puerperium 15 per cent. harboured staphylococcus aureus in their throats and 17 per cent. in the breast milk, and yet their infants came to no harm. While the ubiquity of the staphylococcus ensures that all infants brought up in their natural surroundings come into early contact with the organism, it is clear that this contact is not without risk. This raises problems of immunology which are not dealt with here. It appears that although the staphylococcus aureus is constantly present in the surroundings of the newborn, it is pathogenic to only a few infants. When it is pathogenic to one, however, its virulence is increased

by passage so that other infants are exposed to a more virulent organism. By this means an outbreak of trivial lesions may ultimately lead to an outbreak of virulent infection, as in the cases of pneumonia reported by Smith. Therefore although it is not known why isolated infants succumb to an infection with this common organism, experience suggests that all such cases, however mild the infection, should be isolated to prevent the spread of an increasingly virulent organism and a serious type of lesion.

The specificity of the type of lesion in any one outbreak is interesting. Falls (1917) remarked that in the outbreaks of pemphigus neonatorum observed by him all the lesions were vesicular and the organism, although culturally staphylococcus aureus, tended to appear as a diplococcus on certain media. He suggested that pemphigus neonatorum is due to a specific strain of staphylococcus aureus. Benians and Jones (1929) also noticed the occurrence of vesicular lesions even among the adults infected in the outbreaks described by them, and remarked on the frequent contact of healthy infants with staphylococcus aureus but the rarity of pemphigus neonatorum. They observed no fixed differentiating characters in the organisms isolated from their cases of pemphigus neonatorum from the ordinary staphylococcus aureus. It is remarkable that aerogenous staphylococcal pneumonia has been reported after an outbreak of septic spots but not in a case of pemphigus neonatorum, although the lips and mouth are often affected early. On the other hand the outbreak of pemphigus described by Brewer (1937) was associated with a boil in a nurse and napkin rashes and perionychiae among the infants. It is not clear from the description of the lesions whether they were dome-shaped bullae with clear straw coloured contents or flat vesicles containing frank pus. As far as I have observed, the latter are much less serious and are more akin to superficial septic spots than to true bullous impetigo. In the absence of accurate knowledge of the type of lesion present in these cases, no definite conclusions can be drawn, but all the other evidence available suggests that true pemphigus neonatorum characterized by clear bullae and desquamation exposing the corium, is due to infection with a specific strain of staphylococcus aureus.

There seem to be three clinical types of response on the part of the newly born to the common early staphylococcal infections such as blepharitis and umbilical infection. The most usual is a rapid and complete recovery without any illness and sequelae. Fairly common is the second type of response in which the appetite and weight gain are normal throughout, and there is never any anxiety about the child's general condition, but many septic lesions such as abscesses, otitis media and osteomyelitis may develop in the next few months. This condition is not unlike infantile pulmonary tuberculosis after the age of six months since in both the general condition remains good in spite of an obvious lesion. Also, although the infants are liable to fresh metastatic lesions in any organ and may be left with permanent deformity if the bones are involved, the ultimate prognosis as regards life is excellent unless a rare complication such as pyaemic spread to the lungs, meningitis or secondary infection supervenes. The third type of response occurs in only a few infants in whom resistance to the infection is unusually deficient. In these a dangerous illness follows infection

and is characterized by wasting, a toxic rash, often pyrexia and occasionally a poor appetite. Pus formation is delayed and slight and may or may not be followed by an improvement in the general condition. The condition may fluctuate for weeks or months, and death may finally occur without any apparent cause except toxaemia and with no obvious septic focus. More often after a few weeks suppuration occurs, the weight rises, the temperature falls and the general condition improves. When the child begins to thrive it is usually out of danger. A steady gain in weight in the presence of suppuration is of far better significance than stationary or falling weight with little or no suppuration.

Summary

The clinical types of staphylococcal infections in the newborn are reviewed and the significance and prognosis of each type are discussed. The potential dangers of skin lesions both to the infants affected and to those in contact with them is noted. It is found that the newborn react to staphylococcal infection in a characteristic manner, but as in adults, the infection may be apparently completely localized, bacteraemic or septicaemic in nature. The difficulty of making the diagnosis of staphylococcal meningitis and staphylococcal pneumonia during life, the relative values of clinical bacteriological signs of staphylococcal septicaemia and the absence of reported cases of staphylococcal gastro-enteritis in the newborn are discussed. Anaemia is found to be a late and relatively mild complication of staphylococcal neonatal sepsis, but it persists until the infection is completely localized and may therefore persist long after the neonatal period.

Thanks are due to Dr. J. C. Spence for the personal interest and encouragement he has given to this work and for his valuable suggestions ; to all the members of the staff of the Babies' Hospital for their co-operation and interest ; to Dr. Norton, bacteriologist at the City Hospital for Infectious Diseases, Walker Gate, for all the bacteriological work ; and to Dr. Harlan, Medical Superintendent of the General Hospital, for access to the wards of that hospital.

References

Benians, T. C. H., and Jones, B. H. (1929). *Lancet*, **1,** 174.
Blackman, S. S. (1935). *Johns Hopk. Hosp. Bull.*, **57,** 289.
Bloch, H., and Pacella, B. L. (1938). *J. Amer. med. Ass.*, **110,** 508.
Brewer, D. (1937). *Med. Off.*, **57,** 75.
Cass, J. M. (1940). *Arch. Dis. Childh.*, **15,** 55.
Castle, W. F. (1925). *Brit. J. Child. Dis.*, **22,** 122.
Craig, W. S. (1936). *Arch. Dis. Childh.*, **12,** 171.
Denison, G. A. (1936). *Amer. J. pub. Hlth.*, **26,** 1168.
Devenish, E. A., and Miles, A. A. (1939). *Lancet*, **1,** 1088.
Dilliehunt, R. B. (1935). *Surg. Gynec. Obstet.*, **61,** 96.
Dolman, C. E. (1934). *J. infect. Dis.*, **55,** 172.
Dunham, E. C. (1933). *Amer. J. Dis. Child.*, **45,** 229.
Falls, F. H. (1917). *J. infect. Dis.*, **20,** 86.
Green, W. T. (1935). *J. Amer. med. Ass.*, **105,** 1835.
Grubb, T. C. (1938). *J. Lab. clin. Med.*, **23,** 1150.
Guy, W. H., and Cohen, M. (1929). *Arch. Derm. Syph., Chicago*, **19,** 425.
Kanof, A., Kramer, B., and Carnes, M. (1939). *J. Pediat.*, **14,** 712.
Kelly, F. C., and Dack, G. M. (1936). *Amer. J. pub. Hlth.*, **26,** 1077.
Macgregor, A. R. (1936). *Arch. Dis. Childh.*, **11,** 195.
McCandlish, H. S. (1925). *Amer. J. Obstet. Gynec.*, **9,** 228.
Mount, W. B. (1935). *Ibid.*, **29,** 126.
Seeds, A. E. (1929). *Virginia med.*, **56,** 530.
Smith, C. M. (1935). *Lancet*, **1,** 1204.
Topley, W. W. C., and Wilson, G. S. (1936). *The Principles of Bacteriology and Immunity*, second edition, London, 1268.

VITAMIN K IN PRENATAL PREVENTION AND POSTNATAL TREATMENT OF HAEMORRHAGIC DISEASE OF THE NEWBORN

BY

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Vitamin K is an essential in human nutrition for the maintenance of normal blood clotting function. It is involved in the synthesis of prothrombin and is directly related to the concentration of the latter in the circulating blood. We have (Kugelmass and Samuel, 1931) advanced the hypothesis of a dietary basis of the formation of clotting constituents, formulated 'clotting' and 'bleeding' diets (Kugelmass, 1935a), and applied these in the treatment of amenable haemorrhagic diseases (Kugelmass, 1934). The isolation of the poultry-feed factor in crystalline form (Dam and Lewis, 1937) as vitamin K by Almquist (1937) has led us to determine its effectiveness in haemorrhagic disease of the newborn characterized by diminution in blood prothrombin. This anti-haemorrhagic vitamin is a complex of K_1 derived from vegetable and K_2 derived from animal sources. The potency of each of these compounds has been determined by various methods of assay (Thayer et al., 1939). These data indicate that vitamin K_1 is approximately twice as potent as K_2, the former about 1000 units per mgm. and the latter about 660 units. A unit of vitamin K is defined as that quantity which produces a clotting time of ten minutes or less in half a group of ten or more chicks which have been fed for two weeks immediately following a vitamin K-free dietary.

Vitamin K abounds in the unsaponifiable non-sterol fraction (Dam et al., 1936) of unsuspected sources such as alfalfa, beef liver, bran, breast milk, cabbage, casein, carrot tops, hog-liver oil, kale, mushrooms, peanut, pig-liver fat, rice bran, soy-bean oil, spinach and tomatoes, but is surprisingly absent in such foods as carrots, cereals, cod-liver oil, colostrum, corn, egg white, lemon juice, liver extract, mangoes, potato, rice, rye, wheat germ oil and yeast. This fat-soluble vitamin of dietary origin is absorbed in the intestinal tract in the presence of bile but is completely eliminated in the stool in its absence. Bile salts apparently combine with the vitamin hydrocarbon to enable its diffusion into the intestinal mucosa, otherwise its administration must be supplemented by bile salts, bile acids or desoxycholic acid. It has already been demonstrated that patients maintained on diets devoid of the vitamin for a fortnight

still show a large quantity in the lipoid fraction of the stools as a result of the putrefactive processes by intestinal flora. But vitamin K is normally present in the stools in considerable amounts due to the relatively low efficiency of intestinal absorption.

The metabolism of vitamin K is unknown but its rôle in the synthesis of prothrombin in the bone-marrow and liver is established. The lipoid structures of these reticuloendothelial tissues utilize the fat-soluble vitamin to liberate prothrombin into the blood and lymph which are the immediate sources of this clotting component. Its origin is clear from the experimental studies of Drinker (1916), who obtained prothrombin from megakaryocytes by perfusion of marrow ; of Tait and Green (1926), who extracted prothrombin from platelets ; of Sanford (1938), who found prothrombin in disintegrated platelets ; and of Nolf (1921), who demonstrated the formation of prothrombin in the liver. Indeed, all protein-containing tissues yield the substances necessary for clotting the blood that may be shed through them, but only bone-marrow and liver liberate prothrombin in appreciable amounts into the circulation. Obviously any functional disorders of these tissues may interfere or arrest the formation of prothrombin and lead to the development of haemorrhagic manifestations due to prothrombin deficiency.

Prothrombin concentration

The prothrombin concentration in the blood of normal infants and children remains relatively constant under various conditions. Hundreds of estimations of blood clotting function have demonstrated that nutritional, metabolic, allergic, infectious and endocrine disorders of a non-haemorrhagic nature do not alter the functional level of blood prothrombin. It was determined as the prothrombin index (Kugelmass et al., 1930) which is the ratio of the clotting time of recalcified oxalated plasma of a control to that of a patient. The prothrombin time measured for each has been directly proportional to the active prothrombin concentration in the plasma and only indirectly affected by the concentration of other clotting components. Since this index gives only the intensity factor of immediate value in clotting and not the capacity factor of reserve value, we have also determined the prothrombin content by the method of Warner (1936) expressed in per cent. plasma level of normal children. The values obtained for all age groups after the first year of life are approximately similar and relatively constant in agreement with Brinkhous (1939). As soon as the blood volume has reached about one litre the level of prothrombin becomes that of adult blood.

The prothrombin level of the newborn is about a fourth of that in adult blood (Kugelmass, 1932). This apparent deficiency is not borne out by quantitative considerations, for normal blood contains over a hundred times the amount of prothrombin actually required for coagulation. On diluting the newborn's plasma a hundred times, sufficient thrombin is still produced to

clot fibrinogen within a minute, providing all other clotting components are present in normal amounts. On that basis a drachm of the newborn's blood has enough prothrombin to clot his entire volume of circulating blood while only five drachms of adult's blood will coagulate his total blood volume, although it is about twenty times that of the newborn. The ability of prothrombin to form thrombin is the same in the newborn as it is in the adult, for the clotting time at birth, directly proportional to prothrombin activity, is invariably within normal limits. The prothrombin content undersaturated in the blood of infants during the first few months of life may be increased by the administration of vitamin K in oil. Since there is normally sufficient reserve in prothrombin to fulfil the clotting functions of the newborn's blood, there is no indication to administer vitamin K routinely to bring the prothrombin levels to that of the adult blood. It is only when the prothrombin content of the newborn is diminished, or the clotting time increased, that vitamin K therapy is indicated as a preventive measure. But the reserve level of prothrombin of older infants and children is apparently unaffected by increasing vitamin K intake. An adequate diet thus provides sufficient vitamin K to produce considerably more than the necessary amount of prothrombin to arrest haemorrhage in normal infants and children.

Vitamin K and the haemorrhagic disease

This self-limited syndrome of unknown etiology occurs only within the first week of life. It is characterized by spontaneous haemorrhage, external or internal, in any tissue of the body excluding that associated with trauma, accident or other disease. The condition is relatively rare, and each case differs in the cause and course of its development, but the bleeding is invariably due to prothrombin deficiency in the blood.

I reported ten cases of haemorrhagic disease of the newborn, nine of which showed marked depression in the prothrombin content of the blood with a corresponding lowering in the clotting time (1935b). All other clotting factors were normal—bleeding time, clotting retraction, fibrinogen, antithrombin and platelets, although the rate of disintegration of the platelets was somewhat below normal in some of the cases. Since the determining factor in haemorrhagic disease of the newborn was consistently a decreased blood prothrombin, we designated this condition as acute hypothrombinaemia (Kugelmass and Tritsch, 1934).

The mild form of this disease is undoubtedly self-limited, for two of the ten cases were discovered in the course of routine clotting-time determinations. They showed the characteristic blood features and were treated promptly before bleeding developed. Apparently some cases of potential haemorrhagic disease of the newborn clear spontaneously and thus escape clinical recognition. But severe cases respond poorly to all forms of therapy in spite of diagnosis on the first day of life. These have been associated with prenatal transmission of

the disease indicated by the lowered prothrombin content of the expectant mother's blood.

Such a carefully controlled human experiment consisted of a mother who had given birth to four successive infants with fatal haemorrhagic disease confirmed by necropsies. The recognition of a low prothrombin content during her fifth pregnancy made it possible to bring this to normal levels by the administration of an adequate diet high in fat and protein, apparently abundant in the recently identified vitamin K. The fifth infant was normal and without haemorrhagic symptomatology to date. The sixth pregnancy was characterized by a similar decrease in the prothrombin level, but the mother refused nutritional therapy and gave birth to an infant with severe haemorrhagic disease. During her seventh pregnancy the prothrombin level was raised by adequate diet as during the fifth pregnancy and the infant was normal (Waddel and Guerry, 1939).

Several such cases have been observed with a history of haemorrhagic disease in a previous infant but with a normal blood prothrombin in the mother during the second pregnancy.

A clear-cut case, however, of prenatal prevention of potential haemorrhagic disease was that of an under-nourished woman who had given birth to a proven case of melaena. She was the only member of her family that had showed any bleeding tendency, for since the onset of her menstruation she had occasional nose bleeds, oozing from the gums and mild metrorrhagia and ecchymoses from easy bruising, diagnosed as David's disease. All these manifestations cleared, however, during the previous pregnancy and since the onset of the present pregnancy. At the third month examination of her blood showed a prothrombin index of 0·4, a prothrombin concentration of 30 per cent. and all other clotting components normal. The clotting time was 4 minutes, the bleeding time 1½ minutes, the tourniquet test negative, clotting retraction normal. The low prothrombin level was correlated with a limited dietary of a food faddist, apparently deficient in vitamin K. An accessory bacterial source of the vitamin from intestinal contents was also decreased by the persistent practice of colonic irrigation because of her abhorrence of alimentary toxaemia. An unstable blood clotting mechanism thus became susceptible to vitamin K deficiency, corrected by the administration of the extract in capsules with each meal and adjusting dietary regime to her individual requirements. This readjustment was met with some difficulty, hence the blood was not tested until the sixth month of pregnancy, when the prothrombin approached normal levels. At term, a normal male infant was born without the slightest evidence of haemorrhagic manifestations.

Two cases of haemorrhagic disease of the newborn were recently treated with vitamin K.

In the first case the mother was a primipara with an allergic migraine, maintained on a restricted diet low in protein and fat throughout her pregnancy. An apparently healthy male infant was born without instrumental delivery. On the second day he refused feedings, became restless, vomited dark brown material and showed continuous oozing from the cord. The clotting time was twenty-two minutes, prothrombin index 0·4, prothrombin percentage of normal plasma, twelve. Ten hours after the oral administration of 2 c.c. of vitamin K in oil the bleeding ceased and the clotting time was 10 minutes, prothrombin index 0·8 and prothrombin level 18 per cent.

In the second case the mother, also a primipara with chronic nephritis, was maintained on a restricted dietary low in vitamin K. A female infant born without instrumental delivery was apparently well until the third day, when she developed high fever, vomited after feedings and subsequently passed tarry stools. The clotting time was 17 minutes, prothrombin index 0·5 and prothrombin level 9 per cent. About eight hours after the oral administration of 3 c.c. of vitamin K in oil the bleeding ceased and the clotting time was 5 minutes, prothrombin index 0·7 and the prothrombin level 15 per cent.

Vitamin K administered to two mild cases of haemorrhagic disease of the newborn cleared the condition within twenty-four hours. There was a rise in blood prothrombin and a corresponding diminution in clotting time. Spontaneous bleeding ceased without resorting to other forms of local or systemic therapy more rapidly than expected of a self-limited condition. Vitamin K is thus of equal value with blood transfusion in mild cases, the one forming prothrombin and the other providing it. But mild cases of haemorrhagic disease of the newborn offer no final criteria of the curative value of vitamin K because the co-existence of haematogenous jaundice may diminish absorption and utilization of the vitamin and thus interfere with the synthesis of prothrombin. The ability of vitamin K to raise prothrombin to higher levels in the blood of the newborn is certainly no index of its efficacy in the presence of haemorrhagic disease characterized by injury to the reticuloendothelial system involved in the formation of prothrombin.

Vitamin K is nevertheless a valuable adjuvant in the treatment of latent or active haemorrhagic disease of the newborn. But therapy should not be limited to a precursor of prothrombin when the active substance can be injected into the circulation in the form of a blood transfusion. Certainly there is no indication for the use of vitamin K routinely to protect the newborn from possible haemorrhagic disease because there is ample prothrombin for clotting shed blood. Furthermore, abnormally high prothrombin content cannot prevent blood from oozing through a damaged vascular system unless the entire circulation is clotted ! The contention (Kugelmass, 1933) that the prevention of haemorrhagic disease of the newborn will necessarily diminish intracranial haemorrhage is only partially true, because the former is a disease of the blood and the latter a result of trauma to the vascular system. A normal blood coagulability does not preclude vascular injury and vice versa. Besides, the relative frequencies of haemorrhagic disease and intracranial haemorrhage are about one to twenty and the two diseases are more often mutually exclusive than coexistent.

References

Almquist, H. J. (1937). *Nature*, **140,** 25.

Brinkhous, K. M., Smith, H. P., Warner, E.D., and Seagers, W. H. (1939). *Amer. J. Physiol.*, **125,** 683.

Dam, H., Schonheyder, F., and Tage-Hansen, E. (1936). *Biochem. J.*, **30,** 1075.

——, and Lewis, L. (1937). Ibid., **31,** 17.

Drinker, C. K., and Drinker, K. R. (1916). *Amer. J. Physiol.*, **41,** 5.

Kugelmass, I. N. (1932). *J. Amer. med. Ass.*, **99,** 895.
—— (1933). *N. Y. St. J. Med.*, **33,** 1207.
—— (1934). *J. Amer. med. Ass.*, **102,** 204.
—— (1935a). *Med. Clin. N. Amer.*, **19,** 989.
—— (1935b). *Penn. med. J.*, **38,** 679.
——, Bancroft, F. W., and Stanley-Brown, M. (1930). *Amer. J. Dis. Child.*, **39,** 471.
——, and Samuel, E. L. (1931). Ibid., **41,** 48.
——, and Tritsch, J. E. (1934). *Amer. J. Obstet. Gynec.*, **28,** 259.
Nolf, P. (1921). *C. R. Soc. Biol., Paris.*, **85,** 1116.
Sanford, H. N., and Leslie, E. I. (1938). *J. Pediat.*, **12,** 16.
Tait, J., and Green, F. (1926). *Quart. J. exp. Physiol.*, **16,** 141.
Thayer, S. A., and others. (1939). *Proc. Soc. exp. Biol., N.Y.*, **41,** 194.
Waddel, W. W., and Guerry, du P. (1939). *J. Amer. med. Ass.*, **112,** 2259.
Warner, E. D., and others. (1936). *Amer. J. Physiol.*, **114,** 667.

LINGUAL APPLICATION OF EUMYDRIN IN THE TREATMENT OF CONGENITAL PYLORIC STENOSIS

BY

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A growing interest in the conservative treatment, and especially in eumydrin treatment, of congenital pyloric stenosis seems to have been aroused among British paediatricians by Svensgaard's article in this journal (1935). This treatment has been widely used in Germany and Scandinavia for many years. All those who have employed eumydrin in congenital pyloric stenosis agree that it is usually effective. There is, however, no agreement as to the requisite dose nor as to the mode of application of the drug (Braithwaite, 1937 ; Dobbs, 1939 ; Vertue, 1939).

Before eumydrin was introduced by German physicians, atropine or papaverine was the remedy of choice in the conservative treatment of pyloric stenosis on the Continent and in Scandinavia. These drugs were given by mouth in aqueous solution and in varying doses, and toxic symptoms were rather frequent. Another important disadvantage was the rapid destruction of the drug when dissolved in water. In 1925 Lindberg called attention to the fact that alcoholic solutions of atropine kept their strength and were much more durable than aqueous solutions. Lindberg recommended the use of such alcoholic solution in preference to an aqueous one. In the same article Lindberg recommended giving the alcoholic solution of atropine perlingually instead of by mouth. In Sweden we immediately followed this advice, but in the other Scandinavian countries paediatricians seem to have continued with aqueous solutions given orally.

When eumydrin was introduced, we abandoned atropine and applied the less toxic eumydrin in the same way as we had used atropine; a 0·6 per cent. alcoholic solution of eumydrin (eumydrin 0·3+concentrated alcohol 50) contains approximately 0·1 mgm. eumydrin in each drop. A drop of this solution placed on the surface of the tongue is rapidly absorbed and the treatment and absorption are not interfered with by the vomiting. The doses employed at the Gothenburg children's hospital have been rather small in comparison with the amount of eumydrin given orally in aqueous solution. It has been usual to begin with 1 to 2 drops (0·1 to 0·2 mgm.) daily and gradually increase the dose if necessary until the vomiting becomes less severe. The

earliest sign of toxic effect is a flushing of the face, and if this sign appears the dose is lowered. Usually the vomiting stops or diminishes in intensity before any toxic symptoms develop. It has seldom been necessary to exceed 0·3 to 0·5 mgm. eumydrin daily. This method of application of eumydrin has been employed as a routine treatment of congenital pyloric stenosis since 1928. The mortality rate of the Gothenburg infants suffering from this disease has been 1 per cent. during this period.*

The advantages of this method as compared with the oral treatment of eumydrin in aqueous solution are evident. In the latter mode of application a certain and variable amount of the drug is rejected by the vomiting and thus makes careful dosing impossible. When there is intense vomiting most of the drug is rejected before absorption ; when the infant occasionally stops vomiting for a day or two and the same dose of eumydrin is used most of the drug given is perhaps absorbed. In this way it may happen that sometimes too much eumydrin is absorbed, and although this drug is far less toxic than atropine, it may cause serious intoxication and even death (Monrad, 1938). There is particular danger of this if the solutions are not frequently renewed. One teaspoonful of an old solution does not correspond to one teaspoonful of a freshly prepared solution. The old solution may have been weakened in its eumydrin effect by long standing, and the freshly prepared solution is much stronger, although both solutions originally were of the same strength. If an old solution is finished and the infant is given the same number of teaspoons from a freshly prepared solution and at the same time vomits less, a much larger amount of eumydrin is absorbed than previously, and thus the infant is liable to develop toxic symptoms.

By lingual application of a concentrated alcohol solution of eumydrin the dose absorbed is known and is independent of the severity of the vomiting, whilst the solution keeps its strength without obvious deterioration of the drug. It is clear that toxic symptoms can be prevented much more certainly in this way, and it is on this account that attention is being called to the method which is strongly recommended.

References

Braithwaite, J. V. (1937). *Arch. Dis. Childh.*, **12,** 262.
Dobbs, R. H. (1939). *Lancet*, **1,** 12.
Lindberg, Gustaf (1925). *Acta paediatr., Stockh.*, **4,** 309.
Monrad, S. (1938). *Nord. med. Tidskr.*, **15,** 711.
Svensgaard, E. (1935). *Arch. Dis. Childh.*, **10,** 443.
Vertue, St. H. (1939). *Ibid.*, **14,** 173.

* A communication from Prof. Wallgren, in reply to an editorial query as to the standards of diagnosis, indicates that although importance is attached to the palpation of the pyloric tumour, this is not regarded as the only reliable sign. He states that in his opinion radiological diagnosis is of the greatest value. (*See* Runström, G. (1939), *Acta Paediat., Stockholm*, **26,** 383.)

CASE REPORTS

EXTROVERSION OF THE PRIMITIVE HIND GUT

BY

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Developmental abnormalities should always be of interest for the illustration they may afford of the many still obscure stages in development, and for the challenge they may issue to accepted views on the different stages in organogenesis. The present case is of interest in connexion with mechanism of production of a complicated form of ectopia vesicae.

Clinical history. The third child of an otherwise normal family was born at full term and was referred to hospital. On examination when two days old a most unusual condition was revealed. The baby was small, and the skull, vertebral column and limbs appeared normal. The trunk was normal above the level of the middle of the abdomen. Below this level and situated in the middle line of the anterior abdominal wall was a yellow rounded tumour with blood vessels coursing beneath its surface and forming the base of attachment of the remains of the umbilical cord. This swelling was later represented by a horizontal granulating tissue scar. Below it, and separated by a few millimetres of pale skin, there projected a large, circular mass of red mucosa. Through the central aperture of this prolapsed portion of bowel, faecal material was passed at intervals. More posteriorly, but continuous with this mucosa was a much smaller opening directed upwards and backwards. Immediately behind the smaller opening the perineum was covered by skin and was without dimple or depression to mark the site of any proctodeal ingrowth.

Situated on either side of the larger bowel aperture, but apparently separated at least on the right side by a narrow bar of pale skin, were two areas of red, wrinkled epithelium. From a minute aperture on the left area urine trickled. Just below each of these was a little tubercle covered with pale, smooth epithelium and beneath each of these and forming the anterior part of the perineum was a rounded elevation covered with slightly wrinkled, but normal skin. The infant lived for twelve days taking three-hourly feeds.

Post-mortem examination. By promising to reveal the true sex of the child permission was obtained to carry out a limited autopsy. This was performed within two hours of death. The usual midline incision was carried laterally on each side from just above the middle of the abdomen. After removing the chest organs and liver, the whole peritoneal aspect of the posterior abdominal wall, the pelvic floor with portions of sacrum, coccyx and iliac bones and the lower part of the anterior abdominal wall was taken in one block for

dissection. There was a slight terminal peritonitis owing to spread of infection from the umbilicus. This area, extending as a transverse linear scar, was oedematous and unprotected by underlying muscle and tore readily.

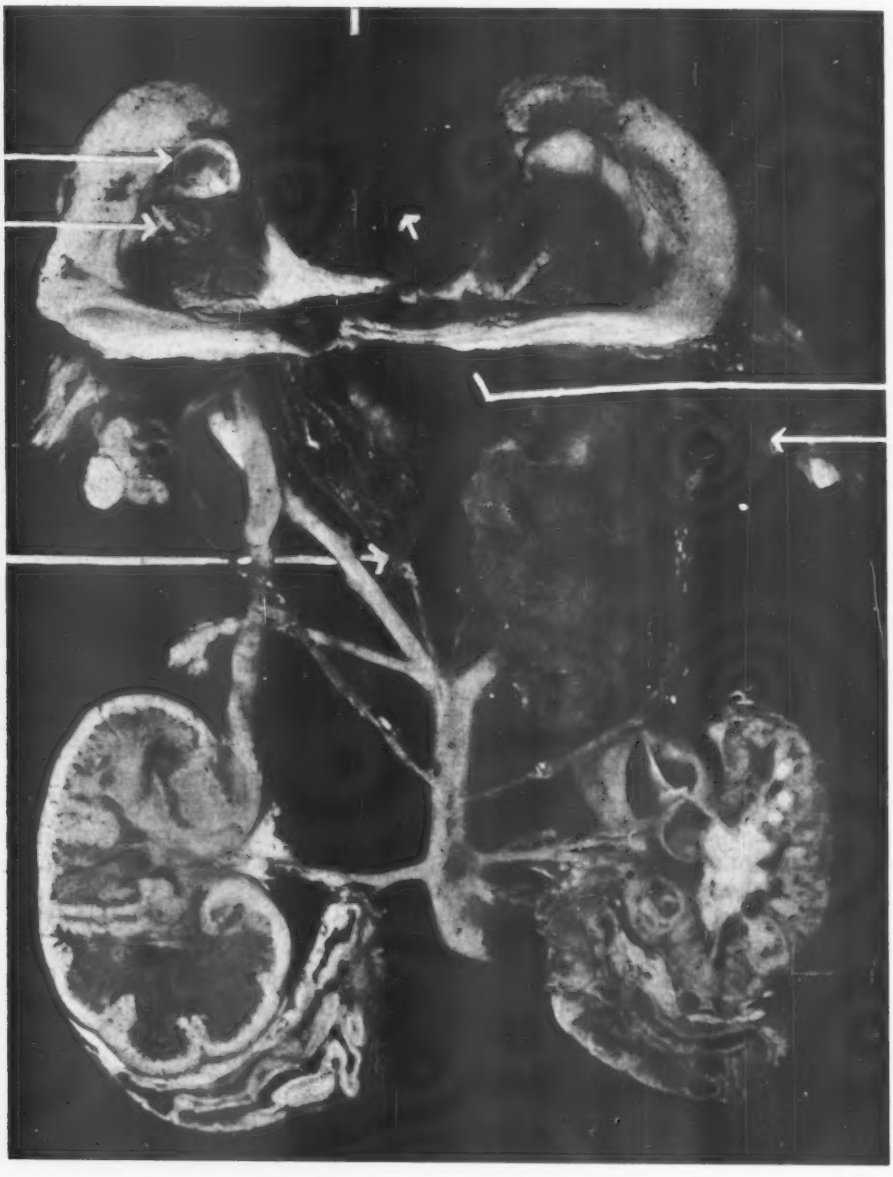

FIG. 1.—Anterior aspect. The structures have been dissected from the posterior abdominal wall. The upper bowel and its orifice are seen and the glass rod marks the opening of the blind inferior tube. s.b. upper portion of bowel opening to exterior on central red area ; inf. mes. A. inferior mesenteric artery supplying the inferior blind tube ; t. testicle ; u.o. left ureteric orifice ; g.t. genital tubercle.

The bowel, normally situated within the abdomen and supplied by the superior mesenteric artery, opened at the large upper aperture in the middle of the anterior abdominal wall (fig. 1). The mucosa was directly continuous with squamous epithelium which intervened between it and the umbilical scar.

The longitudinal muscle was uniformly distributed around the wall. There was nothing resembling a caecum or appendix. Below its orifice was the aperture of the small posterior tube, which was directed backward ; it terminated blindly opposite the upper part of the sacrum and showed no extension even as a fibrous cord. Its artery arose from the anterior aspect of the abdominal aorta just before its division into the iliac arteries, and dividing and forming an arcade, ran in the rather redundant peritoneal mesentery situated somewhat to the left of the tube (fig. 2). The peritoneal cavity extended from the right side round the tube which was only attached to the dorsal abdominal wall along the line of its artery. The superior mesenteric artery supplied the entire extroverted area and a branch ran backwards in the mesentery along the posterior tube to

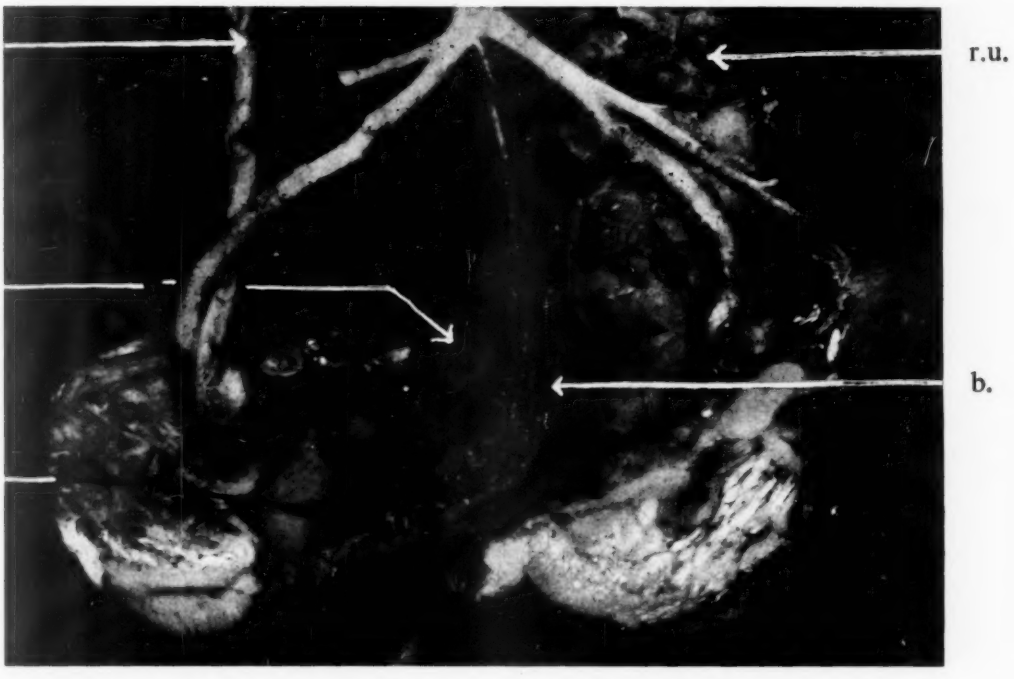

FIG. 2.—Posterior aspect after dissecting away the posterior abdominal wall. The mesentery of the superior part of the bowel is largely cut away. A black thread is holding out the mesentery of the lower blind tube, the artery of which unites with the superior mesenteric artery in this mesentery. A white glass rod marks the orifice of the blind bowel tube. r. and l.u. right and left ureters ; s.b. upper part of bowel ; b. blindly ending posterior tube ; m. thread holding out mesentery of inferior bowel tube.

form an anastomotic loop with the lower mesenteric artery. Histologically, the longitudinal muscle of the two parts of the bowel was continuous. The mucosa of the superior portion of the bowel near its termination showed mucus-secreting cells lining acini and a few well marked villi. The muscle of the lower tube was uniformly distributed around it and the mucosa did not differ significantly from that normal to the large bowel, but submucous lymphoid tissue was present. The superior and inferior portions of the bowel showed continuity of the mucous membrane only at the narrow line of their junction. The mucous membrane of the upper part of the bowel almost encircled the opening of the lower bowel with a wide arm-like extension on each side. A transitional type of epithelium covered the narrow area intervening between the two and the extreme posterior end of the central red area.

The internal iliac arteries each gave off a branch to the lateral red area of their own side and formed the umbilical arteries, both of which were almost obliterated and changed into fibrous cords. The umbilical vessels ran in the retro-peritoneal tissue of the abdominal wall and above the upper bowel opening to the area of scarring representing the attachment of the umbilical cord. From this same area the obliterated strand of the umbilical vein passed up to the liver.

The left ureter and kidney were macroscopically and microscopically normal. The left vas deferens passed round the ureter, dilated slightly, and opened through a minute aperture on the red epithelium just above the small tubercle. The urinary orifice was visible as a tiny slit at a slightly higher level, but rather below the middle of the same lateral red area (fig. 1). The area between the two was covered by a many-layered columnar pseudo-stratified or

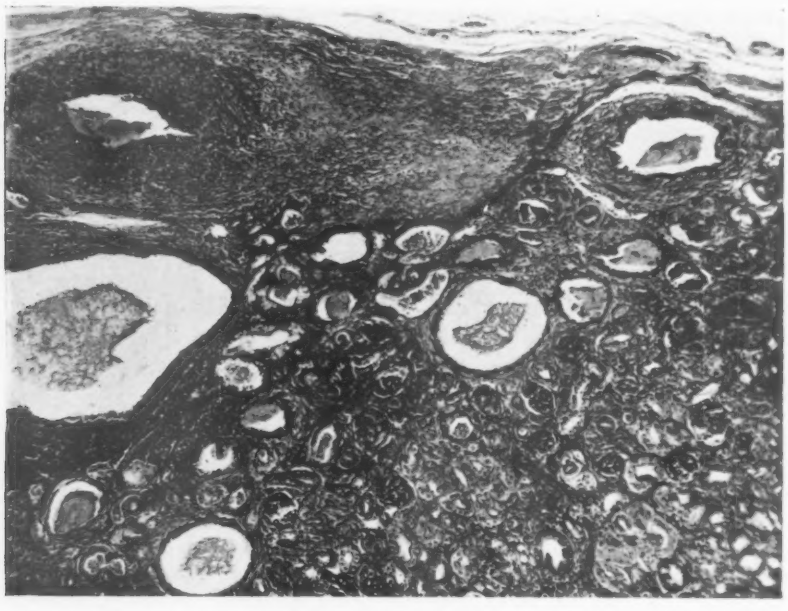

FIG. 3.—The cortex of the right kidney. Some of the smaller cysts are seen and are surrounded by abundant, rather primitive connective tissue.

transitional epithelium differing from the single layer of columnar cells lining the patent sex duct. In the underlying connective tissue and running to open round the orifice of the sex duct where the numerous acini of the accessory sex glands, lined largely by mucus-secreting cells.

The right kidney was pale and reduced in size, and contained numerous small cysts, many of which lay just beneath the capsule. No separation into cortex or medulla was visible. Histologically, the numerous small cystic spaces, varying in size and often arranged in groups, were lined by high columnar or rarely somewhat flattened epithelium and were surrounded by considerable connective tissue of an embryonic type with large, rather vesicular nuclei (fig. 3). There were few properly formed tubules or glomeruli. The renal pelvis was only slightly dilated and was not trilobed. The ureter was enormously dilated and slightly convoluted and provided with a median mesentery ; its lumen was equal to that of an infant's ileum. The lining cells were greatly flattened and almost indistinguishable, and the almost transparent wall was very largely composed of connective tissue. There was, however, an abundant nerve

plexus beneath the peritoneum. The nerve plexuses around the right and left renal arteries showed no significant microscopical difference. The right vas deferens was a solid fibrous cord until it came into relationship with the right ureter. Passing through the medial ureteric wall, which was thickened at this point, it acquired a minute lumen. After communicating with the cavity of the ureter it opened on the right lateral red area in a similar position to the left. A little before its orifice it was surrounded by developing prostatic acini. The ureter had no other opening, but the right lateral red area was similar in size to the left and both, especially the left, showed areas of transition to a squamous type of epithelium. Whilst in some such areas the deeper cells were arranged with their longer axis at right angles to the surface it was often impossible to be certain of any real morphological difference from squamous epithelium. In the underlying connective tissue there were numerous plain muscle cells. Thin walled, dilated blood channels, sometimes containing inflammatory cells were largely responsible for the reddish colour of these areas. Below these areas of extroverted bladder, the forwardly directed tubercles showed a central mass of erectile tissue and on their superior surface were partly covered by transitional epithelium. Histological examination of all the other abdominal, thoracic and neck viscera revealed no abnormality.

Discussion

An explanation must be found for several features of considerable interest. The intestinal tract, supplied by the superior mesenteric artery, opens on the anterior abdominal wall below the attachment of the body stalk and is separated from it by normal skin. The umbilical arteries are normally developed and pass into the stalk from each side above this opening. There is no real development of the bowel below this level, and no attempt to form any connexion with a proctodeal depression. Widely separated from each other by the bowel apertures are the right and left genito-urinary orifices. They open on surfaces covered in part by transitional and in part by squamous-like epithelium. The central red area, whilst largely covered by mucus-secreting epithelium, shows areas of transitional epithelium. Changes, interesting from the viewpoint of comparative morphology, are present in the kidney and excretory ducts of one side.

During the past half century or more a number of somewhat similar cases have been described. Few have been adequately studied histologically and confusion must often exist as to the identity of some structures. This has not prevented many speculations as to the manner of their production and of that of the simpler forms of ectopia vesicae. The value of many of the earlier explanations is reduced by incorrect views about the formation of the bladder. The useful earlier papers are adequately considered by Johnston (1914).

The work of Sternberg (1927) and especially of Florian (1930) on the earliest stages of the formation of the hind gut and on the cloacal membrane is of the greatest interest as providing an adequate explanation for the simpler degrees of ectopia vesicae. The formation of the infra-umbilical portion of the abdominal wall has also recently been studied by Wyburn (1937). It has been shown that in the human embryo the short body stalk is modified to form a part of the sub-umbilical body wall (fig. 4 and 5). This is achieved by a process of differential growth of the embryo whereby this stalk, originally situated at the caudal end of the embryo, comes to arise from the ventral aspect. A portion of the

primitive yolk sac is thus enclosed at the tail end of the embryo and forms the primitive hind gut. There is a very precocious growth of an allanto-enteric diverticulum from the primitive gut cavity into the tissue of the stalk (fig. 4). This represents the primordium of the allantois. Forming the ventral wall of the gut, and for a time extending along this diverticulum on to the stalk is the cloacal membrane. Here ectoderm and endoderm are in contact, but, except where the future excretory passages are to form, should become separated by mesodermal tissue. Keith (1932, 1933) appears to accept the cloacal membrane as the hindermost part of the primitive streak and would accept the membrane as closing the blastophore or primitive mouth and consider that its fission reproduces the mouth of the primitive gastrula or coelenterate ancestor. Wyburn (1937) advances arguments that the primitive streak does not extend so far in the direction of the stalk. The cloacal membrane represents the

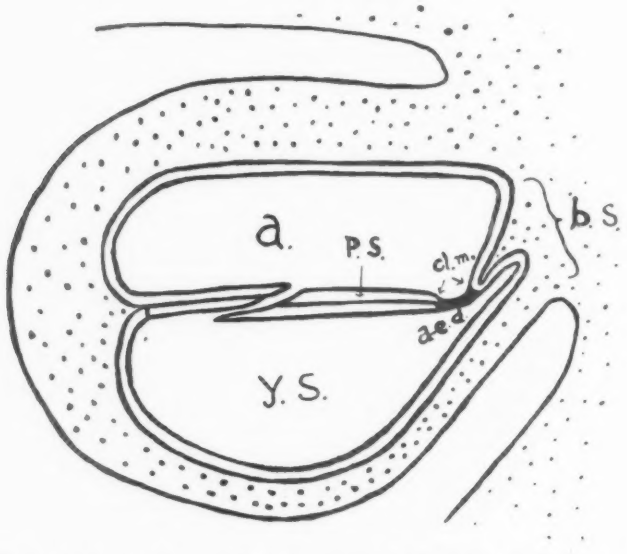

FIG. 4.—A diagram of an early stage of development showing the position of the body stalk and the precocious development of the allanto-enteric diverticulum. a. amnion ; p.s. primitive streak ; y.s. yolk sac ; cl.m. cloacal membrane ; a-e.d. allanto-enteric diverticulum ; b.s. umbilical or body stalk. The extra-embryonic mesoderm is stippled and the whole embryonal formation is suspended in its cavity.

primitive area of contact of ectoderm and endoderm not yet separated by definite mesoderm. Defective development of the mesoderm, especially that derived from the hinder end of the primitive streak, which is less productive in man that in any other form, may result in varying degrees of non-closure. Without the intervention of mesoderm the cloacal membrane will break down.

In the present case the sub-umbilical portion of the anterior abdominal wall is occupied in the mid-line by the openings of the bowel. Normally, apart from the attachment of the yolk sac just above the umbilical stalk, the bowel, except at both ends, is free from the anterior abdominal wall, and is attached only by its dorsal mesentery. It is thus free to develop at a rate disproportionate to the length of the embryo. This is the result of the development of the coelom, and is well described by Frazer (1931). An important stage is the drawing into the embryonic body of a part of the hinder end of the

yolk sac and its relatively excessive growth (fig. 5). This results partly from the relatively excessive growth of the dorsal (neural) aspect of the hinder end of the body producing a relative shortening of the ventral structures. The introduction of the extra-embryonic coelom, between the body stalk with its allanto-enteric diverticulum forming the infra-umbilical part of the anterior abdominal wall and the developing gut caudal to the yolk sac, leaves this latter free to develop and elongate. The term cloaca should be used for the common cavity into which opens the caudal end of the hind gut and the allantois, as the allanto-

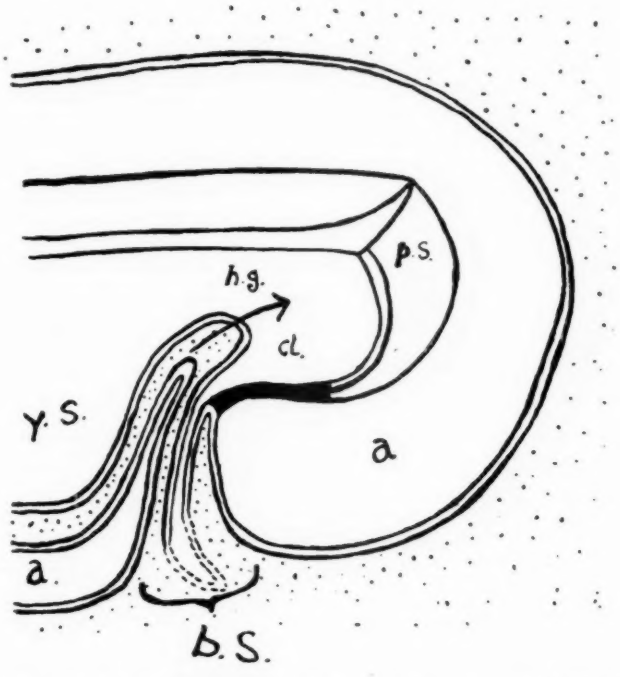

FIG. 5.—The body stalk is now situated on the ventral aspect. The growth of the primitive hind gut behind the yolk sac is beginning and is associated with the formation of the extra-embryonic coelom which will intervene between the adult hind gut and the cloaca and its derivatives. Lettering as for fig. 4, and h.g. area of formation of hind gut ; cl. cloaca into which opens the allantois.

enteric diverticulum may now be called. The term hind gut is applied to the elongating bowel before its lower end enters this common cloaca.

The bowel might open anteriorly at the site of the yolk sac through a persistent vitelline duct. In the present case the umbilical arteries pass above the bowel opening and there is an area of skin intervening between the bowel opening and the body stalk situated above it. There is also no necessary connexion between such a condition and the extroversion of the genito-urinary orifices. The bowel might also communicate with the surface owing to deficiency of the anterior wall of the true cloaca similar to that in a simple extroversion. This would have to be associated with the failure of the cloaca to be divided into anterior genito-urinary and posterior rectal parts by the growth of a mesodermal septum. The upper orifice should then open out of bowel representing the large intestine ; some evidence of a caecum might be expected and it should

be supplied from both mesenteric arteries. The presence of the inferior tube would present insuperable difficulties of explanation as its proximal and not its distal end opens into the cloaca. There is no evidence to support the contention of von Geldern (1924) that this blind posterior tube represents a development and persistence of the post-anal gut.

If the gut caudal to the yolk sac fails to obtain its freedom from the anterior abdominal wall by the development of the extra-embryonic coelom it will be arrested in development. The anterior body wall, if its primitive cloacal membrane persisted, might then break down at any point below the body stalk leaving the bowel to open on to the surface. It is only with persistence of this condition that mechanical theories of overdistension of the cloaca need be considered. (Wood Jones, 1912 ; Russell, 1939). It should be unnecessary to emphasize that without such a primary abnormality, the cloacal membrane cannot rupture to open into any part of the bowel supplied from the superior mesenteric artery without also rupturing across the coelomic cavity. The normal cloacal membrane does not rupture before the second month, but no information is available as to when a more extensive membrane might rupture. In any case purely mechanical distension by urine and faeces (Russell, 1939) is highly improbable. A case described by von Berenberg-Gossler (1913) suggests that such an arrested development of the hind gut may arise without extroversion of the bladder. The ileum communicated by a passage with the bladder and behind this was the caecum, whilst a blind tube suspended from a dorsal mesentery represented the colon.

The condition may thus result from the abnormally early breaking down of the cloacal membrane before any attempted differentiation of the primitive hind gut into a hind gut freed of ventral attachment and a genito-urinary cloaca. No development could then close off a ventral urino-genital from a dorsal alimentary part. This is the view advanced by Johnston (1914). If the cases of Bryce (1895) and Emrys-Roberts (1906) can be taken as comparable, the presence in them of what appears to be a caecal dilation of the upper portion of the bowel suggests that, sometimes, there is some development of the hind gut between the yolk sac and the superior orifice. If no such division of the primitive hind gut occurs the upper bowel opening will correspond closely to the site of the yolk sac, but cannot be considered to be the opening of a vitelline duct as in Sequeira's paper (1896) and Keith's earlier one (1908). A difficulty is to correlate a failure of the extra-embryonic coelom and of the hind gut to develop with the defective formation of the mesoderm of the hinder end of the primitive streak, and its failure to close in the cloacal membrane.

The developmentally arrested portion of gut will retain its blood supply from both the superior and inferior mesenteric arteries. From the dorsal aspect of this primitive hind gut, which should have formed the gut caudal to the yolk sac, a diverticulum may grow into the dorsal mesentery. This will end blindly being without any normal controlling influences. In some cases it may show two small lateral processes considered by Wood Jones (1912) to represent paired appendices. Whether in the circumstances their occurrence is of such morphological significance is more doubtful. In the

present case, and in the cases of Bryce (1895), Doran (1881) and Johnston (1914) no appendix-like structures are present. The upper bowel opening must lie below the body stalk and may be separated by normal squamous epithelium from the umbilical cord. The umbilical vessels can only lie above the bowel orifice.

The lateral walls of the ventral part of the primitive hind gut, which should have become the true cloaca, and on which the Wolffian and related ducts must open, will be pushed to either side of the bowel aperture. If division of the primitive hind gut had proceeded normally the area between these orifices would have formed the dorsal wall of the true cloaca. In simple ectopia of the bladder this is the upper trilobed red area exposed. In the present case, if any attempt at division of the primitive hind gut had occurred, traces of this bladder epithelium might be expected between the mucous membrane of the bowel orifice and the abdominal wall below the stalk. Mucous membrane passed directly into squamous epithelium, but a metaplasia cannot be excluded. Von Geldern (1924) demonstrated intervening bladder epithelium at this site, and in a complicated case described by Russell (1939) a large area of bladder intervened between the umbilical stalk and the orifice of the bowel.

The appearance of the unilateral cystic kidney is not inconsistent with the view put forward by Kampmeier (1926). A metanephric blastema, composed of mesenchyma, forms a cap over a part of each of the branches of the upgrowth from the Wolffian duct. This normally becomes converted into a convoluted tubule and glomerulus, and establishes a junction with the related upgrowth which then forms the collecting tubule. That part of the upgrowth not in relation to the blastema continues to grow and by branching establishes further connexions with the formation of further blastemata. The first few generations should loose their connexion with the collecting system and should atrophy. They may persist as cysts and this may result in a reduction of the number of nephron units. The abundant connective tissue seen in the present instance around these primitive cysts forms a basis for the often enormous increase of interstitial connective tissue sometimes seen in congenital cystic disease of the kidney (Bell, 1935).

The enormously dilated right ureter opens only through the narrow sex duct, which is impervious at a higher level. There is thus a failure even of the first stage in separation of the ureter and Wolffian duct on the right side. This should consist in a dilation of the Wolffian duct and a ' taking up ' of it into the cloaca so that the ureteric orifice may open directly into the future bladder. A further stage is dilation of the lower end of the ureter and its entering into the formation of the bladder wall so that the Wolffian duct is separated from the ureteric orifice. This stage has been attained on the left side. The condition of the right side has been described by Shattock (1895), Sequeira (1895–6) and Wood Jones (1912). It is similar to that normally found in the reptilia, especially in lizards. In the other cases described no cystic condition of the kidney, nor dilation of the ureter is noted. The dilation may be secondary to an almost, but not completely, obstructed urinary outlet. The right kidney is quite capable of secreting urine.

The apparent separation by normal skin of the epithelium of the genito-

urinary areas from that of the gut introduces difficulties. The appearance of the epithelium of the genito-urinary papillae is not inconsistent with a metaplasia. The macroscopic difference is largely determined by dilated blood sinuses. The embryonic line of junction may become invisible with subsequent growth.

The presence of two genital tubercles may be explained. Owing to the deficiency of the mesoderm at this site, the mid-line genital tubercle cannot be formed in front of that portion of the cloacal membrane destined to break down and form the normal excretory outlet of the cloaca. Owing to the wide separation of the parts the lateral genital folds of mesoderm cannot unite to close the deficiency in the membrane posteriorly. The first failure alone would produce epispadias. The case is quite distinct from those of posterior duplicity (Mainland, 1929).

Summary

A case is described of ectopia of the bladder associated with an opening into the bowel from the subumbilical part of the abdominal wall. The mechanism of development of the gut behind the vitelline duct is discussed, and apart from a small blind tube growing into the dorsal mesentery this part of the bowel is considered to be absent. The opening of the primitive hind gut is considered to result from the failure, over almost its entire extent, of the primitive line of junction of ectoderm and endoderm forming the cloacal membrane, to be invaded by mesoderm. This probably resulted from a deficient formation of mesoderm at the hind end of the primitive streak.

Atavistic developmental abnormalities of the right kidney are also present.

A detailed histological study of the exposed areas would suggest that the type of epithelium, other than mucus-secreting, provides no certain criterion for the separation of those parts of ectodermal origin from those of endodermal.

Thanks are due to Mr. Ian Fraser, visiting surgeon to the Belfast Hospital for Sick Children, for permission to report this case ; Professor J. H. Biggart and Dr. R. H. Hunter for advice and encouragement ; and Mr. D. McA. Mehaffey, photographic technician to this department.

References

Bell, E. T. (1935). *Amer. J. Path.*, **9**, 373.
Bryce, T. H. (1895). *J. Anat., Lond.*, **29**, 553.
Doran, A. (1881). *Ibid.*, **15**, 226.
Emrys-Roberts, E., and Paterson, A. M. (1906). *Ibid.*, **40**, 332.
Florian, J. (1930). *Ibid.*, **64**, 454.
Frazer, J. E. (1931). *Manual of Embryology*, London, 50.
Johnston, T. B. (1914). *J. Anat., Lond.*, **48**, 89.
Kampmeier, O. F. (1926). *Anat. Rec.*, **33**, 115.
Keith, A. (1908). *Brit. med. J.*, **2**, 1857.
—— (1932). *Ibid.*, **1**, 488.
—— (1933). *Human Embryology and Morphology*, London, 442.
Mainland, D. (1929). *J. Anat., Lond.*, **63**, 473.
Sequeira, J. H. (1895–6). *Ibid.*, **30**, 362.
Shattock, S. G. (1895). *Trans. path. Soc., Lond.*, **46**, 248.
Sternberg, H. (1927). *Virchows Arch.*, **263**, 159.
Russell, K. F. (1939). *Brit. J. Urol.*, **11**, 31.
von Berenberg-Gossler, H. (1913). *Arb. anat. Inst., Wiesbaden*, **49**, 615.
von Geldern, C. E. (1924). *Arch. Surg., Chicago*, **8**, 61.
Wood Jones, F. (1912). *J. Anat., Lond.*, **46**, 193.
Wyburn, G. M. (1937). *Ibid.*, **71**, 201.

FENESTRAE PARIETALES SYMMETRICAE

BY

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Among the many new diseases which have been described during the present century, there are a remarkable number of diseases of the osseous system. In some instances this is due to the necessity of x-ray examination and biochemical investigation for their diagnosis, but in others, such as osteopetrosis (Albers-Schönberg disease), osteochondrodystrophy (Morquio's disease), gargoylism (dysostosis multiplex), and hypertelorism, these aids were not essential, and it is perhaps surprising that the conditions escaped recognition until relatively late. The rarity of the conditions and the reluctance of writers of textbooks to list them as distinct diseases will also have militated against their general recognition.

In the case of fenestrae parietales symmetricae both causes have been operative. Probably this heredo-familial condition occurs more frequently than is generally supposed, but has received little attention. It is, however, entirely comparable to such a disease as cleidocranial dysostosis, which is widely known, not from personal experience but from its established place in textbooks.

The condition of fenestrae parietales symmetricae is characterized by the presence of symmetrical defects of the parietal bones, situated close together and occurring constantly in the same position. Their site is behind the crown, near the junction of the middle and posterior thirds of the sagittal suture. The defects are of oblong shape, the long axis lying at right angles to the sagittal suture. They vary from ½ to 4 or 5 cm. in length and 1 to 2 cm. in width. The openings are covered with epidermis, and below this the dura can be felt to pulsate as in the anterior fontanelle of infants. Sometimes the openings are connected by a narrow aperture ; there is usually a tendency for them to become narrower. The defect on the right is often somewhat larger than that on the left.

It happens that in the normal skull a few openings are found in the same situation, which are, however, very small. These are the anatomical ' foramina parietalia ' which serve to provide a connexion between the vessels of the galea and the superior longitudinal sinus. Their size is at most a few millimetres, and in many cases they are altogether absent.

In some anatomical museums, skulls with the large openings described above had been observed more than 150 years ago, and Lobstein described them in 1772. In 1919 Pamperl discovered thirty-six cases in the literature, of which five had been described in living persons and the remainder in museum specimens. In 1937 the total number had, according to Voigt, increased to forty-five mostly by observations made on living patients. Amongst these was

one case observed in Holland and described in Dutch by Jonker (1933) under the title ' A congenital skull defect in an infant.' In this typical case the hereditary factor was demonstrable, since the mother of the affected child showed a similar condition though to a less degree. Jonker was also able to observe her patient from the age of eleven months to two years, so that she was able to follow the progress of the defect (see below).

At first these large openings were thought to be variations of the normal foramina, and the name ' foramina parietalia permagna ' was considered suitable. Needless to say, earlier authors suggested various explanations for these large foramina. Increased numbers of blood vessels, or vessels of abnormal size, penetrating the skull were suggested as possible causes, or again local atrophy due to the rapidly growing brain. It is only comparatively recently that the conception of a developmental disturbance in the formation of the skull has held the day. It had been found that the ossification of the parietal bone begins from two centres, an upper and a lower, which centres subsequently grow together to form the parietal tuberosity. Ossification then proceeds radially to the periphery, but in the region of the posterior part of the sagittal suture this occurs less regularly. Shorter and longer osseous ' rays ' alternate so that apertures may arise which are felt in the newborn as Gerdyan fontanelles. The large defects with which we are concerned were therefore explained on this basis, and the term ' foramina parietalia permagna ' retained until recently.

In 1934, however, the subject was illuminated by a clear and well-illustrated article by Zarfl, in which he suggested the simple descriptive name ' fenestrae parietales symmetricae ' for the condition ; this name has since been generally adopted. He pointed out that the term ' foramina parietalia permagna ' was deceptive, since it implied that the openings were identical with the normal anatomical parietal foramina. Zarfl was able to follow accurately for several years the exact course of events in the case of a premature baby. At first there appeared to be a large median bony defect, $5\frac{1}{2}$ to 4 cm. in size, a so-called accessory fontanelle, situated exactly between the two normal fontanelles. By the growth of a median partition in the course of two years this picture changed, and the two typical openings arose. Zarfl was also able to discover the skull of a newborn child in a Viennese anatomical collection which showed a similar accessory fontanelle as a single large orifice. If this child had survived, it would probably also have shown symmetrical fenestrae. When Zarfl, however, claims to have been the first to observe this development of the fenestrae he is in error, since Jonker had preceded him by a year. In Jonker's case, the two openings had already appeared at the age of eleven months, but on the medial side they still remained in direct connexion with the remainder of a lozenge-shaped accessory fontanelle. When the patient was two years old the accessory fontanelle had closed, and typical fenestrae had formed.

Case reports

The present study is concerned with the occurrence of fenestrae in a family of seventeen persons. This family, which comes from a village near Haarlem, consists of a grandfather and grandmother, who are not related ; six children ;

and, up to the present time, nine grandchildren. One younger son is not yet married. In five persons the malformation was demonstrated (see fig. 1 in which pedigree the affected persons are shown in black).

No other congenital abnormalities such as have been described by other authors, viz. tower-head or spina bifida, have occurred in any member of this family. They were not specifically x-rayed for spina bifida occulta, but enuresis did not occur. The affected members of the family were of no special type, and there was nothing to distinguish them in other respects from their

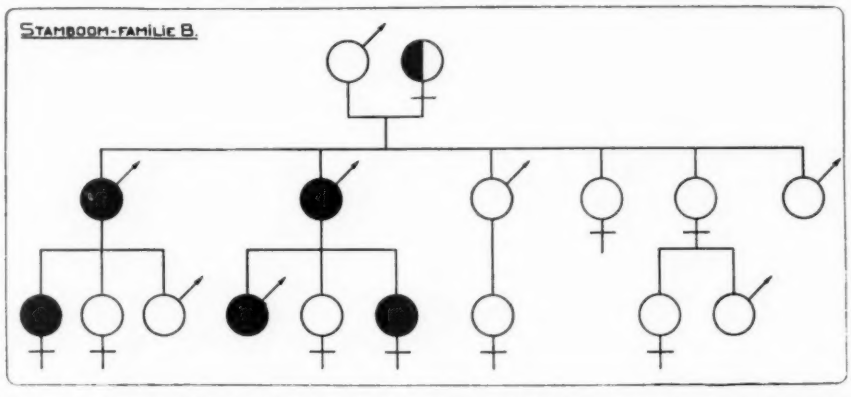

FIG. 1.—Pedigree of family B. showing fenestrae parieteles symmetricae; dark symbols, affected members; the case of grandmother (black-white) is dubious.

normal brothers and sisters, with the possible exception of headache from which they suffered occasionally.

THE GRANDPARENTS, who were born in 1866 and 1876 respectively, did not show the abnormality at first sight. The grandfather is dolichocephalous and has a smooth, well-closed skull. There was no occasion to have a skiagraph made. The grandmother, however, who comes from Zeeland and is brachycephalous, shows on careful palpation a slight bilateral excavation of the parietal bones in the typical situation of fenestrae parietales symmetricae, the dimensions of the depression being 2 or 3 cm. by 4 or 5 cm. These areas, though depressed below the surface, are not compressible and do not pulsate. No fenestrae were visible in the skiagraph of the skull. The latter appeared very solid and slightly acromegalic ; it is not unlikely that previously she had shown skull defects and that the abnormality had come from her side of the family. She had not, however, heard of any abnormalities of the skull amongst her relatives in Zeeland. She complains of pressure on the occiput and rather frequent headaches. In the pedigree she has been indicated as a doubtful case.

Of their six children, the first two sons both show the defect ; two younger sons and two daughters are exempt from it. Amongst the grandchildren, the defect has so far only occurred in the children of the two eldest sons.

HARK B., born 1895, the eldest son, is a sturdy man, in whose skull the two small pulsating openings can be distinctly felt. He was passed for military service, but probably at that time the affection (which he had not mentioned) was overlooked. He has few complaints, and only of recent years on excessive exertion has he been aware of a ' heavy feeling ' in his head in the region of the fenestrae, which he imputes to the latter. On x-ray examination, two fine fenestrae are visible, which, however, are smaller than those of his brother. The edges are smooth (see fig. 2).

He has three children, of which only the eldest, a girl, GERDA, born in 1922,

FIG. 2.—Hark B., father to Gerda. Age 42 years.

FIG. 3.—Gerda B., daughter to Hark. Age 17 years.

shows the defect (fig. 3). In her case the openings are almost round. She has no symptoms related to them.

DAAN B., born 1889, the second son of the grandparents, is likewise a sturdy man. He was exempted from military service after the family doctor had drawn the attention of the examining physicians to the affection. The bone-defects are with him relatively large, but they cause him little trouble, though they pulsate strongly ; pressure on the spots, for example during a hair-cut, is disagreeable to him, and he also has sometimes a spontaneous and peculiar pain in his head, which he distinguishes from ordinary headache, and which he localizes in the defects ; this pain appears when he is tired. His

FIG. 4.—Daan B., father to Arie and Catherina. Age 41 years.

FIG. 5.—Arie B., son to Daan. Age 7 years.

skiagraph is typical ; the edges of the openings are crenated, and also the opening on the right side is the larger (fig. 4).

About the three children of this son I can be somewhat more circumstantial, because it was possible to submit them to a regular medical examination.

ARIE B., a boy born in 1932, was first seen in 1935 with general symptoms. He was then three years old, suffered from chronic infections, and had enlarged tonsils. His skeleton was strikingly slender. The skull already showed the complete fenestrae with a closed anterior fontanelle. Over the two skull defects a distinct pulsation was felt, which has become progressively less obvious in the course of time, so that now (1939) it is hardly recognizable. On x-ray examination (October 1939) the typical defects are nevertheless to be seen as large holes (fig. 5). The opening on the right is larger than that on the left.

FIG. 6.—Catherina B., daughter to Daan. Age 1¾ years.

JANNA B., the second child of this father, born in 1934, appeared to be free from the affection, and no defects were visible on x-ray examination.

CATHERINA B., the youngest child, born in 1938, was first examined at the age of four weeks. There was at that time a large fontanelle with posteriorly a widely patent sagittal suture. This latter merged posteriorly with two lateral defects, lying laterally and communicating with each other, thus forming a T (fig. 7). As the child appeared exudative, I saw it repeatedly, and was on each occasion able to mark out the shape and size of the defects. At the age of about a year, a separation arose between the vertical and transverse portions of the T. The vertical portion of the T had gradually begun to assume a dumbbell form (fig. 7b), and at the age of sixteen months, the anterior expansion of the space represented the anterior fontanelle, and the posterior expansion an accessory fontanelle. Unlike the cases seen by Zarfl and Jonker, there was here no connexion between the accessory fontanelle and the oblong opening from which the fenestrae subsequently arise.

When the child was one and three-quarter years of age, the anterior portion of the skull showed little change, but posteriorly a small bony partition could

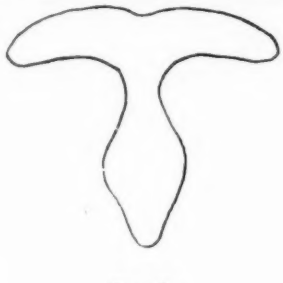

FIG. 7a.

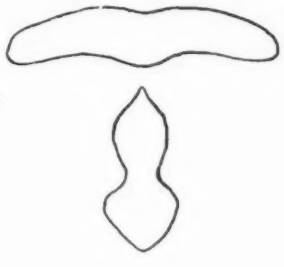

FIG. 7b.

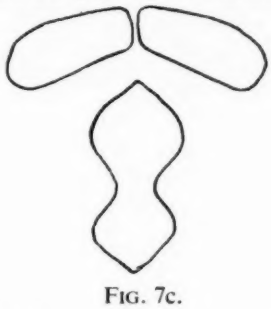

FIG. 7c.

7a. The T-shaped skull defect at the age of 4 weeks of Catherina B.

7b. The transverse defect is loose from the dumbbell shaped front. The fenestrae still connected. Age 16 months.

7c. Formation of the two fenestrae by intergrowth of a narrow partition. Age 1¾ years.

be felt, in the mid-line, dividing the oblong opening into a right and left half (fig. 7c). The bony division was ½ cm. broad. The skiagraphs were hard to interpret, but in fig. 6 the large defect is well seen, though nothing is yet visible in this picture of the narrow bony division mentioned above. Thus it appears that the fenestrae arose from the division of a congenital defect of the skull of much greater size. This was not, as in the cases described by Zarfl and by Jonker, a large accessory fontanelle but a T-shaped defect.

Discussion

Both an hereditary and familial incidence of the condition had been observed by Neurath in 1922, a mother and two of her three children being affected in one instance and a mother and her only child in a second. Before then only one hereditary case appears to have been described, that of Symner (a father and son). Since 1930 other examples of the condition occurring in parents and children have been recorded (Lelong and Bosquet, 1932 ; Häszler, 1936 ; Wissler, 1938). In most of these later publications, Zarfl's description ' fenestrae parietales symmetricae ' has been employed.

The best observation, however, is that of Voigt (1937), who was able to study a family of fifteen persons in which the abnormality occurred in three generations. Marquézy (1939) also recently described ' lacunes congenitales de la voûte cranienne ' in an infant, the mother, and the maternal grandfather. The present description of this Dutch family is closely comparable to that of Voigt. What distinguishes this family from most foreign observations is the absence of other congenital abnormalities.

Summary

A family of seventeen persons is described, five of whom showed fenestrae parietales symmetricae, whilst one individual (the grandmother) showed depressions in the same situation in the parietal bones. Other congenital abnormalities were not present in the family. The older members of the family complained of vague headaches.

In the case of one of the grandchildren, the condition could be observed from the age of one month, when the openings were already present as the transverse portion of a T-shaped cranial defect. The communicating fenestrae were not separated by a median bony division until the age of one and three-quarter years.

The term fenestrae parietales symmetricae (Zarfl) is considered preferable to the older description, foramina parietalia permagna.

The condition is probably not uncommon.

References

Häszler, E. (1936). *Mschr. Kinderheilk.*, **64,** 337.
Jonker, A. (1933). *Maandschr. Kindergeneesk.*, **3,** 80.
Lelong, M., and Bosquet (1932). *Bull. Soc. Pédiat. Paris*, **30,** 161.
Lobstein, quoted by Voigt (1937).
Marquezy, R. A. (1939). *Nourrison*, **27,** 294.
Neurath, R. (1922). *Z. Kinderheilk.*, **32,** 121.
Pamperl, R. (1919). *Dtsch. Z. Chir.*, **148,** 91.
Symner, quoted by Voigt (1937).
Voigt, R. (1937). *Mschr. Kinderheilk.*, **70,** 224.
Wissler, H. (1938). *Arch. Kinderheilk.*, **115,** 217.
Zarfl, M. (1934). *Z. Kinderheilk.*, **57,** 54.

THE IMPORTANCE OF BRONCHOSCOPY IN THE RECOGNITION OF NON-OPAQUE FOREIGN BODY IN INFANTS AND CHILDREN

BY

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When the presence of a non-opaque foreign body in a main or lower lobe bronchus is suspected, the following radiographs will be required, in addition to screening in order to note the positive movements of the mediastinum, heart and diaphragm : (1) A postero-anterior view at the end of inspiration ; (2) a postero-anterior view at the end of expiration ; (3) a lateral view ; and (4) occasionally a bronchogram.

Radiographs of the normal chest when in full inspiration and full expiration show that the following points can be noted : (1) An increased translucency of both lungs during inspiration ; (2) the position of the heart, mediastinum and the trachea is unaltered and in the mid-line ; (3) the dome of the diaphragm is depressed with inspiration and rises with expiration ; (4) the intercostal spaces are widened with inspiration ; (5) the apices of the lungs are contracted in inspiration ; and (6) a decreased translucency of the lungs in expiration. When one lung is in the condition of ' obstructive emphysema,' the affected lung remains hypertranslucent at the end of expiration, due to the trapped air being unable to escape, and in a suspected case of a non-opaque foreign body radiographs in both inspiration and expiration are essential.

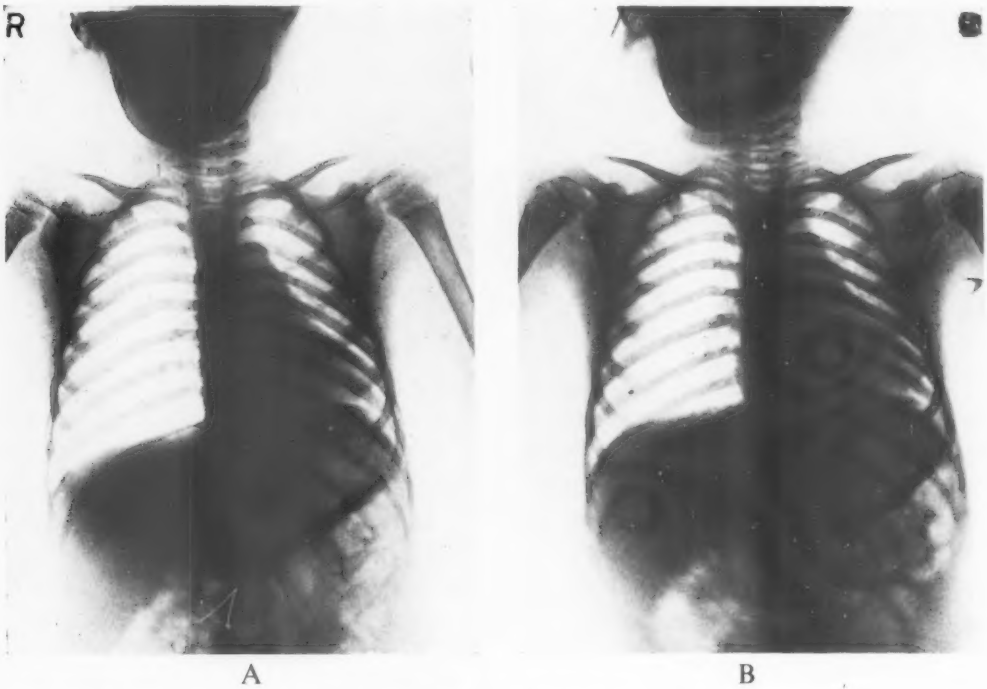
Case reports

The following case records emphasize the diagnostic and therapeutic value of bronchoscopy in suitable cases.

Case 1.—Non-opaque foreign body (pea-nut kernel) blocking the left main bronchus ; bronchoscopy with clearing of the bronchus ; subsequent sojourn of portion of a pea-nut for over twelve months in the left lower bronchus, with no symptoms pointing to its presence, except persistent localized physical signs at the left base ; removal of a pea-nut by bronchoscopy twelve months after inspiration ; recovery.

H. L., aged five years, was admitted in September, 1937, with dyspnoea following the ' swallowing ' of a pea-nut kernel twenty-four hours before.

The child was flushed, not cyanosed, with a hoarse voice and a slight dry cough. Temperature 101° F., respirations 32. Movements were diminished over the left chest, especially at the base. A pleural rub was heard over the left chest in front. Radiographs of the chest taken at the end of inspiration and expiration showed a greatly diminished air entry to the left lung (see fig. 1, A and B).



A B

FIG. 1, A and B. (Case 1.) Pea-nut in left main bronchus producing obstructive atelectasis. Radiographs at the end of inspiration (A) and end of expiration (B) before bronchoscopy, September 4, 1937.

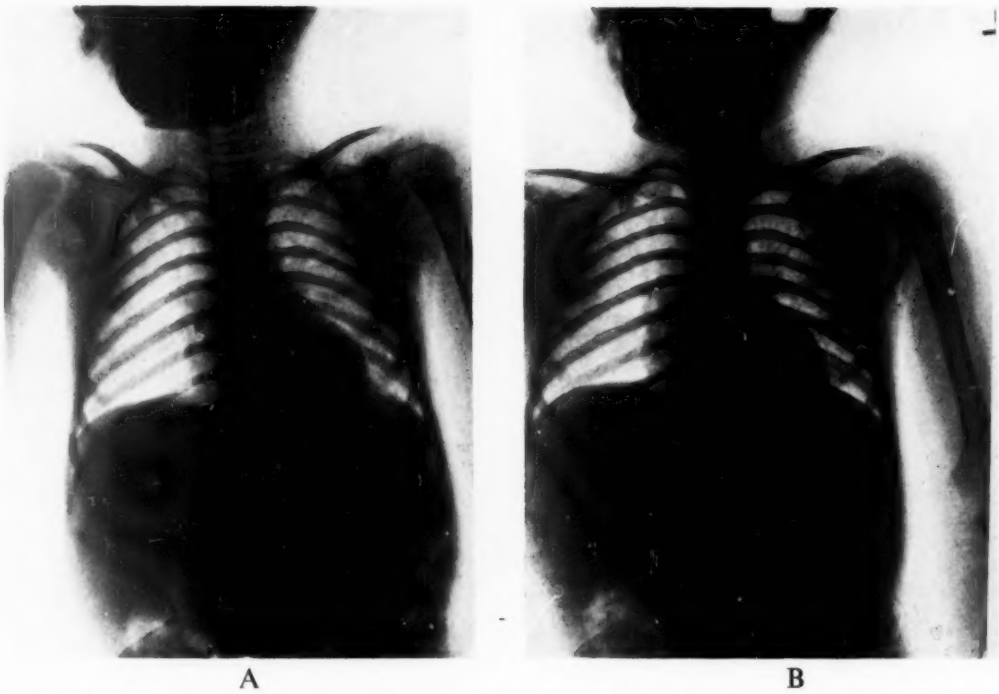
The heart and mediastinum were pulled over to the left, so that the right border of the vertebral column was exposed. The left dome of the diaphragm was raised, and remains so in full inspiration. The heart, trachea and mediastinum shadow were drawn over more to the left on inspiration and receded slightly to the right on expiration when the right border of the heart became visible at the right border of the vertebral column. The aeration of the left lung was not altered at the end of inspiration and of expiration. These radiological signs were caused by a left-sided atelectasis.

The same radiological picture is also consistent with ' obstructive emphysema ' of the right lung, a condition due to impaction of a foreign body in the right main bronchus causing a ball-valve obstruction in which air can pass into but cannot pass out of the obstructed bronchus. The lung tissue becomes hypertranslucent at the end of the inspiration as well as at the end of the expiration. However, in this case the foreign body was found in the left bronchus.

Bronchoscopy was performed on September 4, 1937, under chloroform anaesthesia, using the 5-mm. Jackson instrument. The left main bronchus was cleared of mucus, but no foreign body was seen.

SUBSEQUENT COURSE.—Within three days the temperature became normal ; the breathing was good ; rhonchi were heard all over the chest ; air entry was equal on both sides ; the heart reverted to its normal position. A skiagraph

on September 13, 1937, showed the lungs filled with air equally and the diaphragm was normal (fig. 2, A and B).



A B

FIG. 2, A and B. (Case 1.) After bronchoscopy: lungs clear. Similar pictures were obtained on January 3, 1938, and September 19, 1938.

LATER PROGRESS.—The child remained well, with occasional bouts of coughing, but no other symptoms, and if a routine three-monthly examination of the chest had not been ordered the child would not have been brought for advice. Radiographs on January 3, 1938, and September 19, 1938, showed no abnormality. On each occasion on which the chest was examined at the three-monthly routine visit a slightly diminished air entry was detected at the left base, with a sonorous expiratory rhonchus persistently localized to an area the size of a shilling, and sounding like an expiratory squeak. The child was admitted for observation, and during five days in hospital the temperature was normal and there was no coughing. Radiographs were negative. On deep inspiration and expiration, coarse râles and crepitations could be heard at the base.

On September 22, 1938, under chloroform anaesthesia, using the Negus infant instrument, bronchoscopy was repeated. The trachea and right main bronchus were normal. The left main bronchus was normal, but at its depth a pool of yellow pus was observed, filling the left lower lobe bronchus. This pus was aspirated, and a portion of pea-nut became visible. It was removed in fragments by a forward-grasping forceps, with the use of a sucker in between. The nut was friable and fragmented easily. The bronchus was finally cleared. The macerated portions removed are shown diagrammatically in fig. 3. A piece of nut was found at the end of the aspirating tube, and many small pieces in the receptacle of the sucker. The time taken was twenty minutes. Within one hour of the bronchoscopy the left base had a normal air entry and percussion note, and the expiratory squeak had disappeared. In June, 1939, the child was still well and the left base clear.

Comment.—This case illustrated that persistent signs at the base of a lung should lead to exploratory bronchoscopy. In this case part of a pea-nut had remained in a lower lobe bronchus for over a year with little or no symptoms and only slight signs. It also indicates the necessity for repeated routine exami-

1 2

FIG. 3.—Portions of the macerated pea-nut—part 1 removed by the aspirating tube and rescued from the sucker bottle ; part 2 removed by the forceps.

nations of the chest after bronchoscopy for a suspected non-opaque foreign body, when that body has not been completely removed. Failure to locate it by bronchoscopy is no final evidence of its absence, unless this is substantiated by the clinical examination of the chest at subsequent regular intervals.

Case 2.—Non-opaque foreign body (piece of egg-shell), blocking the right main bronchus of an infant ; bronchoscopy ; recovery.

T. S., aged eleven months, was admitted on June 20, 1938, with the history that five days previously he was playing with some broken egg-shells in his pram. His breathing was noticed to become suddenly distressed and when picked up he started a hacking cough which went on for five minutes. The infant did not go red in the face, was well for an hour, and then started another bout of coughing. He became distressed at night and was thought to have pneumonia. He was better during the day and relapsed at night. The respiration became noisy and asthma was then diagnosed. The noisy respiration persisted.

On admission he showed noisy and distressed respiration. Temperature 102° F., pulse 162, respiration 64. There was apparent laryngeal obstruction, with recession of the intercostal spaces on inspiration and excessive abdominal breathing, but no cyanosis. Dullness elicited over the entire right side of the chest with diminished air entry at the right base suggested massive collapse of the right lung. Skiagraphs of the chest (fig. 4) showed the heart and mediastinum drawn over to the right and the diaphragm raised on the right with collapse of the right upper and middle lobes.

On June 21, 1938, under chloroform anaesthesia preceded by seconal bronchoscopy was performed using the Negus suckling instrument. Pus welled up through the glottis and was sucked away ; the trachea also contained pus. Aspiration revealed an acute congestive laryngitis, tracheitis and bronchitis. .The right main bronchus was filled with pus which was aspirated and the lumen cleared. No foreign body was actually observed. Immediately after bronchoscopy, which lasted twenty minutes, the breathing was easier and the air entry was equal on both sides. A relapse occurred after return to the ward, and the respiratory embarrassment returned till the next day, when improvement followed vomiting. Respirations 40, temperature 103° F., pulse 92. June 23, temperature 99° ; respirations 30. June 24, the child was convalescent ; skiagraphs showed equal air entry (fig. 5).

FIG. 4. (Case 2.) Before bronchoscopy.

FIG. 5. (Case 2.) After bronchoscopy.

Case 3.—Unsuspected non-opaque foreign body (pea-nut) in the right bronchus for over three months producing relapsing collapse of the right lower lobe ; removal of pea-nut at bronchoscopy ; recovery.

G. C., aged 6½ years, was admitted on December 29, 1937, with a history of a cough for three weeks, worse for the last four days. On admission the temperature was 101·6° F., pulse 136, respirations normal. Breath sounds were faint and there was an impaired percussion note at the right base.

FIG. 6. (Case 3.) On admission, December 30, 1937, showing triangular shadows due to collapse of lower lobe of right lung.

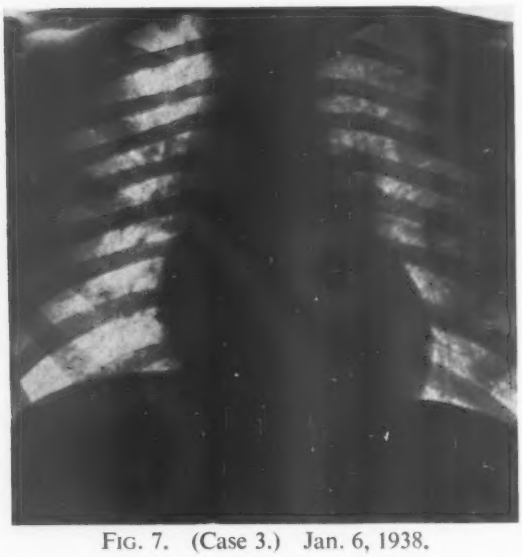


FIG. 7. (Case 3.) Jan. 6, 1938.

A radiograph (fig. 6) showed the typical triangular shadows produced by collapse of the lower lobe of the right lung. The right diaphragm was raised on screening. Mantoux test negative. The temperature settled in five days ; there was no cough.

A radiograph on January 6, 1938 (fig. 7) showed the chest clear, and as there were no abnormal physical signs he was sent home.

Re-admitted on February 18, 1938, the child had been well until seven days before, when he became feverish. Cough which had been present for three

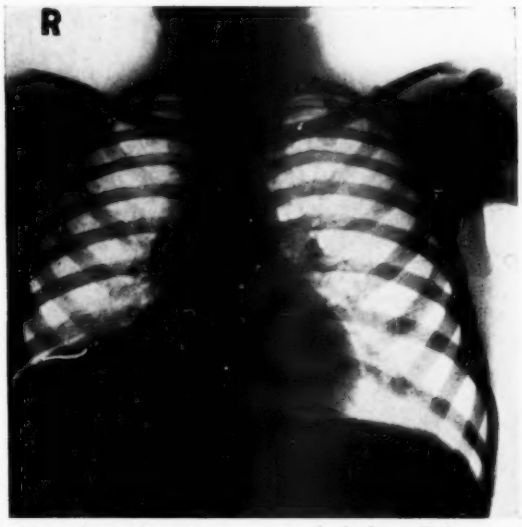


FIG. 8. (Case 3.) Before bronchoscopy, on readmission, February 21, 1938, still shows shadows due to collapse of middle and lower lobes of right lung.

weeks was severe for the past week, with much sputum. The right base showed diminished movement and poor breath-sounds and impaired percussion note.

A skiagraph on February 21, 1938 (fig. 8), again showed collapse of right middle and lower lobes. A diagnosis was made of recurrent collapse due either to enlarged mediastinal glands or to intrabronchial obstruction. Tuberculosis

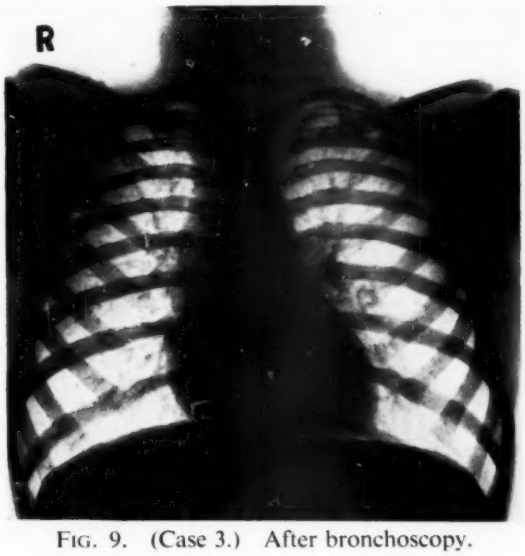


FIG. 9. (Case 3.) After bronchoscopy.

was excluded by a negative Mantoux test. A bronchogram revealed an obstruction in the right main bronchus just beyond the bifurcation.

On March 31, 1938, under chloroform anaesthesia a bronchoscopy was performed (using the child's Negus instrument) and a pea-nut kernel was removed intact from the right lower lobe bronchus. The pea-nut was unchanged by its prolonged sojourn in the bronchus. The time taken was five minutes ; recovery was complete.

This patient was under the care of Dr. Sidney Owen.

Comment.—The skiagraphs taken at intervals show the collapse and re-expansion of the right middle and lower lobes. The variations in the x-ray findings show that repeated clinical and x-ray examinations are necessary to enable a competent opinion to be given, as in Case 1. There was no history of an inhaled foreign body in this case. A skiagraph on April 2, 1938 (fig. 9), showed no abnormality and there were abnormal physical signs in the chest.

GENERALIZED ANGIOMATOSIS PRESENTING THE CLINICAL CHARACTERISTICS OF STORAGE RETICULOSIS

WITH SOME OBSERVATIONS ON THE RETICULO-ENDOTHELIOSES

BY

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During recent years a considerable and increasing interest has been displayed in those disease conditions which show proliferative changes in the reticulo-endothelial system, and to which, in German literature, the name of reticulo-endotheliosis has been given. Such changes can be evoked by many different stimuli and whereas some forms of activity are hyperplastic and reactive, others are neoplastic in nature; thus they may occur in the presence of abnormal lipoids or as the result of infection and blood destruction, or as proliferative changes of a neoplastic nature, e.g. Hodgkin's disease and certain leukaemias. In a paper published a few years ago, Abt and Denenholz (1936) maintained that the grouping together of such heterogeneous conditions under one heading 'reticulo-endotheliosis' did not present any advantage either for clinical diagnosis or for pathological classification, and at first sight the case here recorded supports their view, since the condition found at autopsy was entirely different from the clinical diagnosis of a storage reticulosis. The different incidents in this case will be described in chronological order, a method which illustrated the way in which the diagnosis varied from time to time and the steps by which the final clinical diagnosis was reached.

Case report

On March 6, 1934, V. D., a girl aged fourteen years, was referred by her doctor to a surgical colleague, Mr. F. A. R. Stammers, for an opinion as to the nature of a swelling of the upper part of the sternum which had appeared suddenly about a month previously. The swelling had not increased much in size during this time, but six months before a similar swelling had appeared and subsided. The lump, which was about the size of a filbert nut, appeared to arise from the lower part of the left sterno-clavicular joint and gave a feeling of fluctuation with doubtful egg-shell crackling at one point. The condition was regarded as due to either tuberculosis or syphilis, or as being a myeloma. A

radiological examination of the sternum was made by Dr. C. G. Teall, who reported as follows: ' Bone destruction and rarefaction in manubrium, ? tuberculous.' Shortly afterwards the child was admitted to a nursing home for the removal of the tumour and it was then discovered that she also had a greatly enlarged spleen. At operation the tumour did not show any resemblance to tuberculous osteitis or a myeloma, but consisted of an air-containing cyst in which were present spicules of bone and some blood. A histological examination of a portion of the tumour was made by Prof. Haswell Wilson, who stated that ' sections show dense fibrous tissue with areas of transition to cartilage and some islands of calcification and imperfectly formed bone. There are some foci of chronic inflammation, round cell infiltration and old haemorrhage; nothing suggestive of myeloma or tuberculosis.'

On March 23 she was admitted to the General Hospital, Birmingham, for further investigation. At this time the spleen almost reached the middle line and the crest of the ilium and an indefinite lump was palpable below the liver. The child was pale and a blood count showed a definite degree of orthochromic anaemia (table 1). A few days later, one of us (L. G. P.) was asked to see her and made the suggestion that her condition was due to a ' reticulo-endotheliosis.' On the assumption that the lump below the liver was a mass of glands, Hodgkin's disease was regarded as the probable form of reticulo-endotheliosis; nevertheless, to exclude the possibility of aleukaemic leukaemia another differential leucocyte count was done, and the long bones were x-rayed. The differential count showed a few immature lymphocytes and myelocytes (table 1), and the report on the x-ray photographs was as follows: 'Similar changes (we presume to those in the sternum) in the humeri, femora, tibiae and right fibula—Hodgkin's disease ' (C. G. Teall).

On April 13 the patient was transferred to the Children's Hospital under the care of one of us (L. G. P.) and at this time, apart from the pallor, she did not appear to be ill. Both the girl and her mother, but not her father, had somewhat Jewish features, although a Jewish ancestry could not be traced. The child was fairly well developed although secondary sexual characters were not present. On examination of the abdomen, in addition to the large tumour having all the characteristics of an enlarged spleen, there was an indefinite soft mass in the right subcostal area which was apparently continuous with the liver. The liver itself was enlarged, felt soft, and its lower border could not be accurately determined. Free fluid was not demonstrated in the abdomen and there were no abnormal signs in the chest. There were no tumours palpable in the long bones and indeed, apart from a cloud of albumin in the urine, nothing else was found on physical examination. The Wassermann reaction was negative. Skiagraphs of the long bones showed various areas of decalcification having the appearance of cysts in the upper ends of both humeri (fig. 1 and 2) and of the right fibula (fig. 3), the upper ends (particularly the necks) and also the lower ends of both femora (fig. 4). These skiagraphs were described as being consistent with a diagnosis of Hodgkin's disease. A skiagraph (antero-posterior) of the chest showed ' much shadowing in the lower two-thirds of the right lung field and an appearance of consolidated areas and cavities ' (fig. 5), and a lateral view showed consolidation of the right upper and middle lobes. The appearance of the lung skiagraphs was so strikingly similar to that seen in a case of the Christian-Schüller syndrome which had recently been under our care that the question as to whether this case was an example of Gaucher's splenomegaly with bony deposits was immediately raised. A blood count at this time showed a hypochromic anaemia, and the red blood cells showed some anisocytosis. In spite of the fact that up to this date the results obtained from biochemical examination of the blood (table 2) had been essentially normal, it was thought the child might be suffering from Gaucher's disease and therefore

TABLE I

BLOOD COUNTS

DATE	HGB. PER CENT.	RED BLOOD CELLS PER C. MM.	COLOUR INDEX	WHITE BLOOD CELLS PER C. MM.	POLYMORPHS PER CENT.			LYMPHS. PER CENT.	MONOS. PER CENT.	REMARKS
					NEUT.	EOS.	BASO.			
23.3.34	50	2,570,000	0·98	5,200	69·0	1·6	0·6	22·6	6·2	
29.3.34				6,040	67·0	1·6	1·2	21·2	3·6	Myelocytes—2·0. Immature Lymphs. 3·4.
16·4·34	69	4,190,000	0·82	12,250	62·7	0·7	1·3	29·4	6·0	Anisocytosis. Vol. per cent., 72. Vol. Index, 0·87. ? Microcytosis. Sat. Index, 0·96.
29.5.34				6,500	79	1	0	13	7	R.B.C. Normal
4.4.35	70	3,680,000	0·95	7,500	69	2	1	22	6	Crenation of R.B.C. noted in counting chamber and films, which were all carefully prepared.

PRICE-JONES CURVES—

21.4.34. M.D.—7·11μ. The curve showed slight spread to the right, the largest cell measured being 10·5μ

4.4.35. M.D.—7·04μ. The curve was within normal limits in every respect.

FIG. 1.—X-ray picture of upper end of right humerus showing cystic changes.

FIG. 2.—X-ray picture of upper end of left humerus showing cystic changes.

TABLE 2

BLOOD CHEMISTRY

DATE	1.4.34	10.4.34	17.4.34	3.5.34	28.5.34	27.6.34	4.10.34	4.4.35	10.4.35	FLUID IN BLOOD SPACES 14.5.35
	MGM. PER CENT.	MGM. PER CENT.	MGM. PER CENT.	MGM. PER CENT.	MGM. PER CENT.	MGM. PER CENT.	MGM. PER CENT.	MGM. PER CENT.	MGM. PER CENT.	MGM. PER CENT.
Total fatty acids	329	559		591	518				559	246
Total cholesterol	188	211	148	400	171	213	130		211	126
Phospholipoids	180	167		350	214		308		167	196
Urea			29		33					87
Non-protein nitrogen			31		34					61
Amino acid nitrogen			13·1		10·2	7·6				8·2
Uric acid			2·1		2·4					7·4
Creatinine					1·28					1·9
Calcium				10·6	10·7			9·5		8·7
Phosphorus				2·6	2·5			3·8		20·0
Phosphatase					11·1					
Van den Bergh				0·7 units	0·4 units					
Chlorides										485
Albumin										319
Globulin										2·3
Fibrin										0

The normal values for blood lipoids (mgm. per cent.) in children according to Erickson, Williams, Hummell and Macy (1937) are: Total lipoids, 336.606 (average 454); total cholesterol, 126.281 (average 182); phospholipoids, 51.175 (average 126).

FIG. 3.—X-ray picture of upper ends of tibiae and fibulae showing cystic changes, particularly at upper end of right fibula.

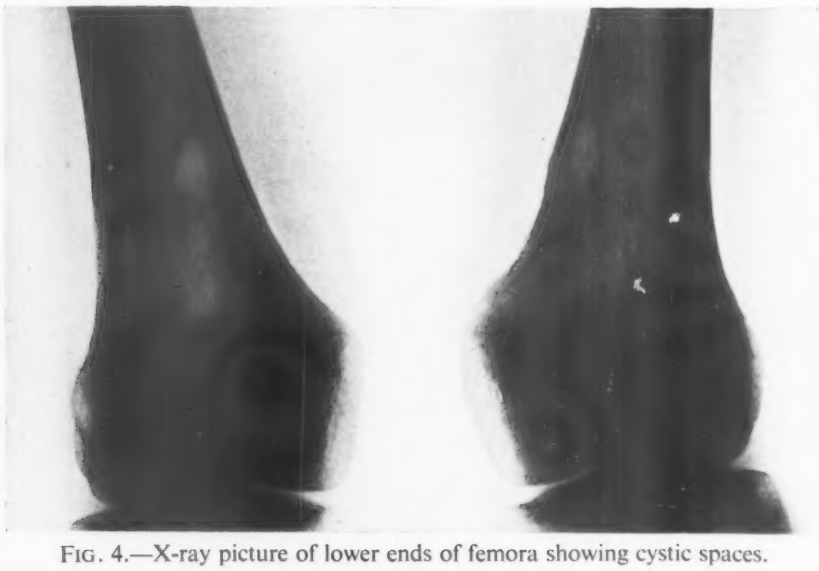

FIG. 4.—X-ray picture of lower ends of femora showing cystic spaces.

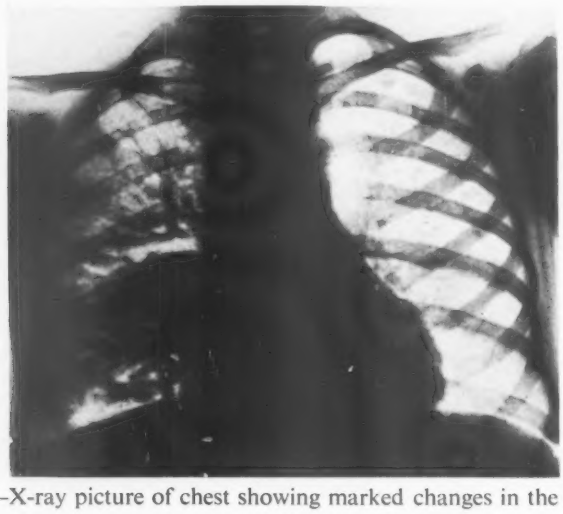

FIG. 5.—X-ray picture of chest showing marked changes in the right lung.

further sections from the tumour removed at operation were examined by the late Dr. R. J. Gittins, who reported as follows: ' Sections of marrow show no abnormal marrow cells. There is much fibrous infiltration around the vessels which show some fibrosis of their coats. The picture suggest a chronic inflammatory reaction but there are no distinctive or characteristic features. Syphilitic infection appears possible.' Gaucher cells were not seen in the sections. Pigmentation of the skin and the wedge-shaped pigmentation of the cornea (pingueculae), which are features of Gaucher's disease, were absent and slit lamp examination of the eyes did not reveal any abnormality.

The presence of a normal percentage of cholesterol in the blood did not necessarily exclude a lipoid disease, because the blood cholesterol is frequently low in Gaucher's disease and may be normal in patients suffering from the Christian-Schüller syndrome despite the fact that the abnormally stored lipoid in that disease is a cholesterol ester; moreover the total lipoids and phospholipoids in the blood have been found to be normal in proved cases of Gaucher's disease (Pachman, 1938). Nevertheless, further investigations were carried out and on May 3, 1934, high values for blood cholesterol and phospholipoids were obtained (table 2). These findings were regarded as strong evidence in favour of a lipoidosis and the diagnosis of Gaucher's disease was accepted. At this time, also, the blood calcium and phosphorus were estimated and were found to be 10·6 and 2·6 mgm. per cent. respectively, the latter being a somewhat low value, the normal at her age being about 3 mgm. per cent. The immediate direct Van den Bergh reaction on the blood serum was negative, the delayed reaction was slightly positive and the indirect showed 0·7 units of bilirubin (0·2 to 0·5 normal).

Because of the diagnosis of Gaucher's disease, x-ray treatment to the spleen was started and the child was discharged on June 22, 1934, but continued to attend the out-patient department for x-ray treatment until April 1935. During this time further biochemical examinations of her blood were undertaken and radiographic changes appeared in the vertex of the skull, the pelvis, the upper ends of the tibiae and the left fibula (see fig. 6 to 10), but her general condition

FIG. 6.—X-ray picture of the skull showing small areas of rarefaction in the vertex.

did not show any deterioration, although the abdomen enlarged slightly as a result of further enlargement of the liver and spleen.

* Fig. 6 to 10 were taken six weeks before death and one year after fig. 1 to 5.

FIG. 7.—X-ray picture of upper end of femora showing extensive changes in neck of the right femur.

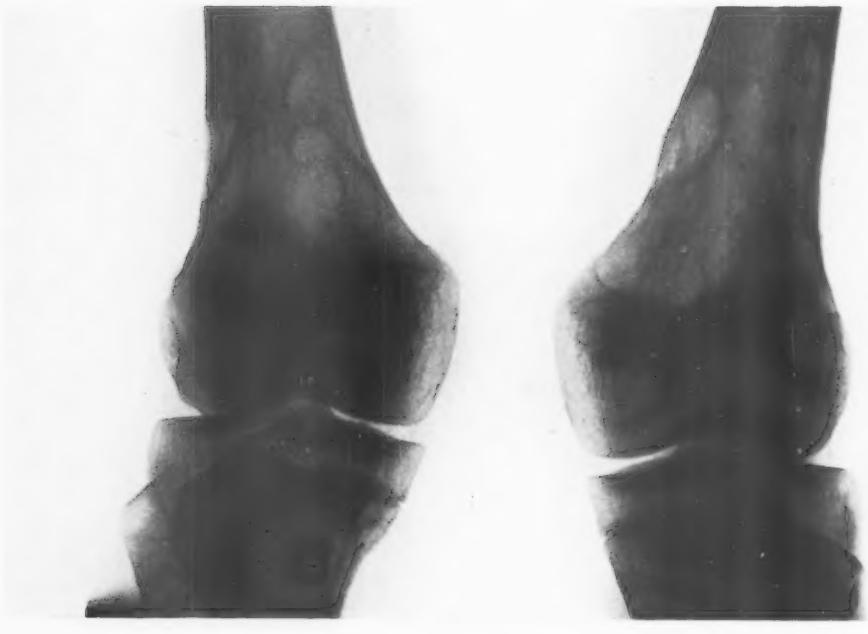

FIG. 8.—X-ray picture of lower end of femora for comparison with fig. 4.

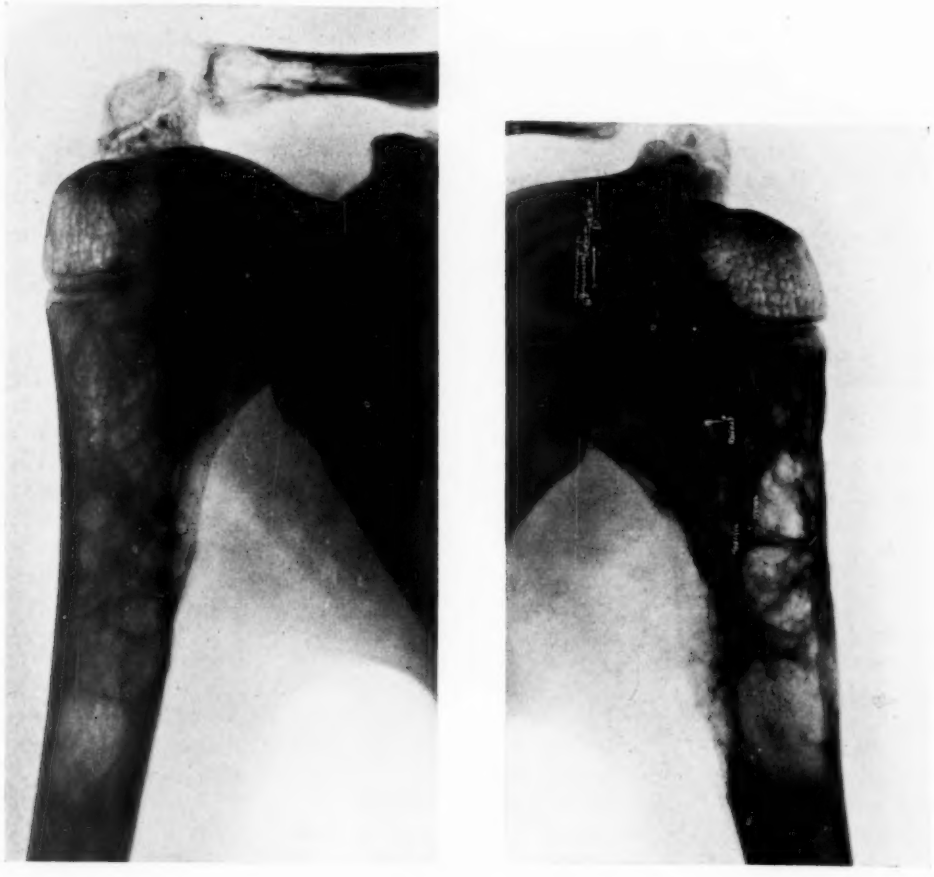

FIG. 9 and 10.—X-ray picture of right (fig. 9) and left humerus (fig. 10) showing an extension of the changes seen in fig. 1 and 2.

Differential diagnosis. The points which during this child's life seemed to justify the diagnosis of the 'osseous form of Gaucher's disease' can be summarized as follows: an enormous degree of splenomegaly, hepatomegaly, infiltration of the lung, cystic areas and tumours in the long bones, an abnormal condition of the blood lipoids, hypochromic anaemia, a Jewish facial appearance, good nutrition, normal blood calcium, the absence of a palpable parathyroid tumour and also of Bence-Jones protein in the urine. It is true that the following characteristics of the disease were absent: family history, Jewish parentage, pigmentation of the skin, brownish pingueculae, persistent leucopenia, the club-shaped appearance of the lower ends of the femora in the skiagraphs, foci in the mandible, and Gaucher's cells at biopsy of the tumour. The absence of these signs is, however, not as important as at first sight might appear to be the case. For instance, the disease does not always show a familial incidence, nor are the patients invariably Jewish; skin pigmentation is absent in 25 to 55 per cent. of the cases and pingueculae are among the rarer manifestations of the disease. The skiagraphic appearances in the bones in the present patient are like those figured by Abt and Bloom (1928) in a case of Gaucher's disease and are also similar to those sometimes found in the Christian-Schüller syndrome. They are strikingly similar to the bone changes described by van Creveld and Poorten (1935) in a child which during life was thought to be an example of

the Christian-Schüller syndrome, but which did not show any evidence of that disease at autopsy, and which they classified as an infective reticulo-endotheliosis. An interesting point in this connexion is that during the lifetime of the present patient skiagraphs of her lungs and bones were shown to Professor van Creveld who expressed the opinion that the condition was a form of the Christian-Schüller syndrome. Leucopenia is always stressed as an important sign in Gaucher's disease, and both it and the anaemia have been regarded as due to the presence of Gaucher cells in the marrow (myelophthisic anaemia). This view is not accepted by Castle and Minot (1936), and if indeed this be the true explanation of the blood changes it is extraordinary that leucopenia is not characteristic of all forms of storage reticulosis; actually the opposite sometimes happens. Thus, leucocytosis has been described in Niemann Pick's disease, in Gaucher's disease itself and in other forms of reticulo-endotheliosis. Gittins (1933) has given good reasons for believing that the changes in the reticulum in haemolytic anaemia and in storage reticulosis are reactive in nature and that sometimes reticulum cell proliferation and argyrophil reticulin fibril formation may replace marrow tissue and result in the production of an aplastic blood picture. Such a view furnishes a more reasonable explanation of variations in the blood picture in the various forms of reticulo-endotheliosis than the one which regards them solely as a mechanical result of the presence of masses of storage reticulum cells. In the present case the majority of the white cell counts ranged between 5,200 and 7,500, although they have reached 12,250 per c.mm. (table 1). The most formidable argument against the diagnosis of Gaucher's disease was the absence of Gaucher cells in the biopsy of the sternal tumour, but it was thought that this was because these cells had been squeezed out of existence by the excess of fibrous tissue; such a state of affairs is known to occur, since Brill and Mandelbaum (1913) have shown that during the course of Gaucher's disease there is a tendency for the Gaucher cells to elongate and later to disappear and to be replaced by intercellular fibrosis.

Weighing up all the evidence, therefore, it was felt that the points in favour of the diagnosis of the osseous form of Gaucher's disease considerably outweighed those against it, and this diagnosis was therefore accepted. It will be noted that a diagnostic splenic puncture was not made, the reason for this being that we have never been completely satisfied about the safety of this procedure. Although the findings at autopsy rudely shattered any feeling of pride in our diagnostic acumen they did at least furnish the consolation that this caution in the matter of splenic puncture was completely justified. The child did not attend the hospital after the middle of April 1935, and on May 12 of that year she died suddenly during the night. During the day before she had developed fever, cough, and difficulty in breathing. A post-mortem examination was performed by one of us (J. H. E.) at her home on May 13.

Autopsy summary

Female, aged fourteen years, height 5 feet. The extremities were slightly wasted and there was a small healed operation scar over the upper part of the sternum. The abdomen was very prominent, the circumference at the umbilicus being 31·5 inches. The skin showed a purpuric rash consisting of numerous small, bluish-black nodules, varying in size from one millimetre to one centimetre in diameter, some of the larger ones being slightly raised. Some of these nodules had the appearance of extravasated blood, whereas others were naevoid in appearance showing slight dilatation of small capillaries. They all appeared to be of recent origin.

In the abdomen the liver was found to occupy the whole area exposed

extending from the costal margin to the symphysis pubis, and measured fourteen inches long by fourteen inches wide. The two lobes were well defined by a prominent fissure. The most striking feature, however, was the presence of a large number of dark cysts on the surface which varied in size from minute swellings to the size of a hen's egg; these cysts were purplish-black in colour and contained thin, blood-stained fluid (fig. 11 and 12). Dense fibrous adhesions

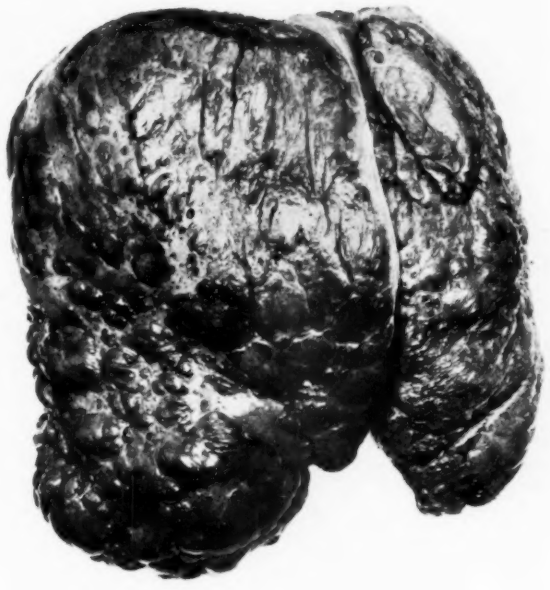

FIG. 11.—Anterior surface of liver showing multiple cysts.

bound the upper surface of the liver to the diaphragm and several cysts were ruptured during its removal from the body. The cut surface of the liver (fig. 13) presented the appearance of a large irregular sponge, the cystic spaces being of an angiomatous nature and forming a complete network throughout fully four-fifths of the liver substance, the only recognizable liver tissue remaining being a small, pale, yellowish red area in the central zone. Except for dense adhesions the gall-bladder appeared normal.

The spleen (figs. 14, 15 and 16), which was pushed to the extreme left side of the abdominal cavity by the liver, was unusually large, reached the brim of the pelvis and measured 10 by 6¼ by 5 inches. It was firm with a dark greyish-green mottled surface, and there were dense adhesions between its antero-superior surface and the parietal peritoneum. The cut surface was fibrous and showed an irregular network of cystic spaces with thick walls, some of which were filled with thin serous fluid, others with dark blood, and still others with a milky, gelatinous material. Here and there recent small haemorrhages were seen.

A large retroperitoneal mass measuring 6¾ by 7 inches, was found beneath the left lobe of the liver; this had its origin in the region of the root of the mesentery and consisted of several large, thin-walled cystic spaces which ruptured during removal and discharged a thin sanguineous fluid. The peritoneal cavity contained several ounces of blood-tinged fluid.

FIG. 12.—Posterior surface of liver.

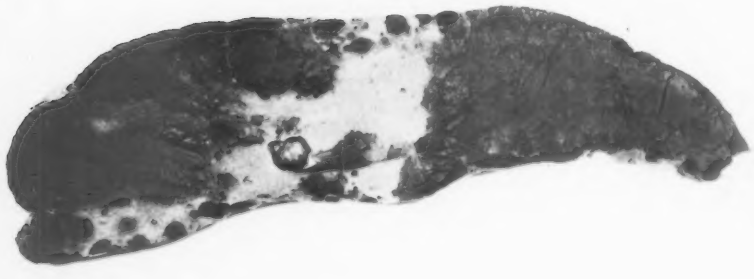

FIG. 13.—Cut surface of liver showing large area involved by the formation of cysts, only a small central portion being free of them.

Both kidneys were normal in size, soft in consistency and presented a mottled surface due to the presence of numerous brownish-black haemorrhagic areas in the cortex, all of which appeared to be of recent origin.

On opening the thorax about three ounces of thin pinkish fluid were found in each pleural cavity. The left lung was dark reddish-grey in colour and showed marked congestion and early broncho-pneumonia but there were no cystic changes to be seen. The right parietal pleura showed several small blood cysts hanging from its surface. The right lung presented many firm, fibrous adhesions over the posterior surface of the base and apex, was reddish-black in colour and showed numerous angiomatous cysts on its surface. There was little normal lung tissue recognizable, all the lobes showing evidence of marked congestion,

FIG. 14.—Anterior surface of spleen.

FIG. 15.—Posterior surface of spleen.

FIG. 16.—Cut surface of spleen.

a dense network of cystic spaces, and considerable fibrosis. The bronchi contained thick mucus, but there was no evidence of their dilatation nor of involvement by the cystic changes.

The thymus gland was prominent and consisted of two lobes. The left lobe showed no change, but the right consisted of multiple cavernous angiomata filled with dark fluid blood.

The pericardium presented several cysts over its surface; clusters of these were seen in the region of the origin of the great vessels and presumably arose from mediastinal lymph glands. The heart showed no evidence of involvement by the process and presented no gross abnormalities.

BONES. The posterior portion of the eighth rib on the right side showed an area of tumour formation two inches in length, dark greenish-black in colour, and involving the whole thickness of the rib. This area was soft, allowed free bending of the rib at this point and consisted of numerous thin-walled cystic spaces, filled with blood-stained fluid. Similar lesions were noted in the seventh rib on the right side and smaller lesions in the fifth and seventh ribs on the left side. The manubrium sterni was thickened and the cut surface showed empty cystic spaces having thin walls and confined to an area in the region of the left sterno-clavicular joint (fig. 17). Similar lesions were found in the neck of the right femur. The other bones were not examined.

No gross abnormalities were detected in the other organs.

Microscopical examination. SPLEEN. Numerous pieces of tissue taken from different parts of the organ were examined and all the sections revealed a similar picture (fig. 18). The general structure was sponge-like in nature, with cavernous angiomatous spaces occupying about two-thirds of the spleen. These cavernous spaces varied in size from quite small to large spaces, some of which were filled with blood and others with clear serum. A few had lost their contents or had not

FIG. 17.—Upper surface of manubrium sterni showing cystic spaces beneath original operation site near left sterno-clavicular joint. (Natural size.)

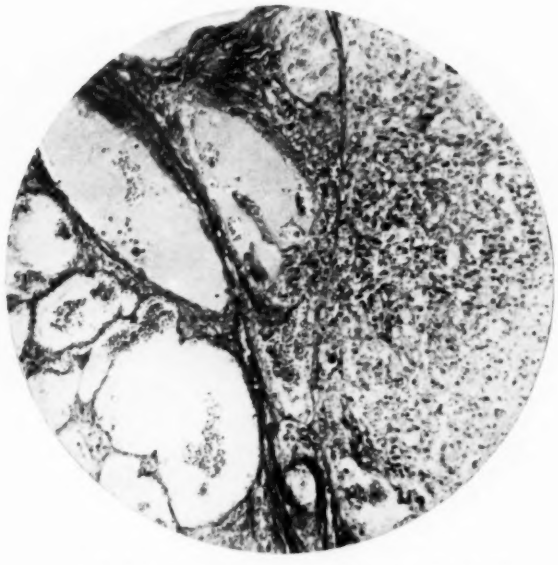

FIG. 18.—Spleen, showing arrangement of angiomatous spaces (× 95).

been filled. Some of the spaces were separated by thick fibrous septa, whereas others were separated by a thin layer of cells and all were lined by endothelial cells. The nuclei of the endothelial cells varied in size and shape, some being round and lightly stained with granules, while others were long and darkly stained; the latter were more frequent in the thick wall where fibrous tissue had formed. In the remaining areas of spleen the splenic pulp showed fairly marked congestion.

LIVER. There were extreme variations in the size of the cavernous spaces which contained red blood cells, fibrin and a few leucocytes with a relative increase of the polymorphonuclear cells (fig. 19). In a few spaces there was evidence of post-mortem thrombus formation. The septa varied greatly in thickness from those consisting of a single layer of large spindle-shaped endothelial cells to those (fig. 20) which were thick, having a lining of long endothelial cells. There was much collagen and fibrous tissue present in the septa. The lining cells besides being long, had long pale nuclei. A few cells showed two nuclei but there were no mitotic figures and they did not appear malignant in the usual histological sense. The large septa showed papillary projections and contained small capillaries.

LUNGS. Both lungs showed considerable congestion, the alveoli contained a few blood cells, numerous large pigment-containing ' heart-failure cells ' and

a few leucocytes (fig. 21). Scattered areas, especially at the surface, contained small cavernous angiomata with thin walls formed by a single layer of endothelial cells (fig. 22). Sections taken from the root of the right lung revealed a

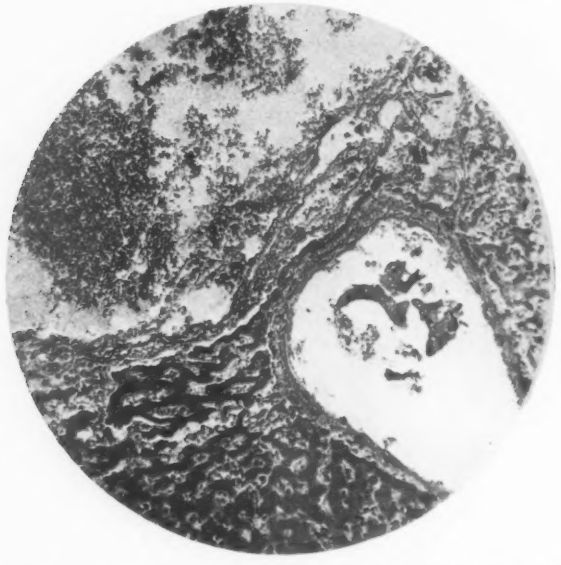

FIG. 19.—Liver: large cavernous space at edge of comparatively normal liver tissue (× 95).

FIG. 20.—Liver: thick septum dividing a large angiomatous cyst (× 420).

more chronic invasion of the lung tissue by angiomata. Here the cavernous spaces were large with thick fibrous walls, communicating with each other but no communications were found with normal blood vessels or with bronchi.

KIDNEY. Sections taken in the areas which appeared haemorrhagic in the gross specimens showed normal kidney tissue being invaded by small cavernous spaces. The glomeruli and tubules were compressed and in some places

flattened out between two septa of these spaces. The septa were lined by the same long endothelial cells seen in the sections of other organs. The process of formation and spread of the cavernous spaces appeared to be of recent origin since none was large and many glomeruli and tubules appeared normal.

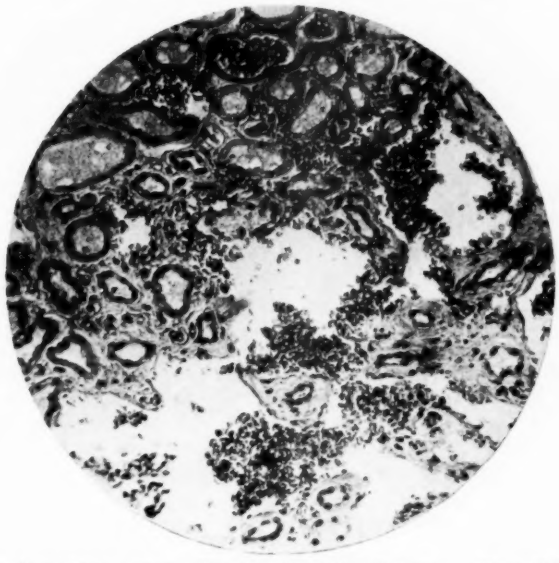

FIG. 21.—Lung: angiomatous spaces showing fibrosis of septa. Alveoli filled with red blood cells and fibrin (× 100).

FIG. 22.—Lung: wall of angiomatous space shown in fig. 22, showing long lining endothelial cells.

Recent extravasations of blood were seen between the tubules which had not been reached by the process (fig. 23).

Sections of thymus and bone showed cavernous angiomata similar to those described in other organs.

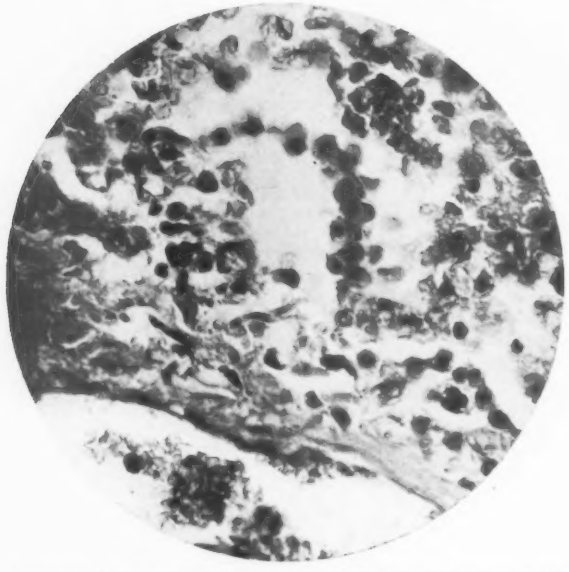

FIG. 23.—Kidney: haemorrhage and early spread of tumour between tubules. A few tubules remain isolated and surrounded by spaces which are lined by a layer of young endothelial cells (× 100).

Site of origin of angiomata

In the literature angiomata are described as usually arising in the liver or the spleen, and more rarely in the thymus, skin, lung, bone marrow and retroperitoneal glands. It has been impossible to determine the site from which the tumour arose in the present case; at first it was thought to be the spleen, but further study of the liver and the large retroperitoneal mass showed that these had probably been involved for as long a period of time as the spleen, and although it is true that the largest masses were found in the spleen, liver and retroperitoneal glands, there was considerable tissue involved in the lungs, the thymus, many of the bones, the pericardium and pleura. The degree of involvement of any one organ, therefore, does not help in solving the riddle of the site of the tumour.

The onset and character of the chief signs and symptoms are usually determined by the organ primarily affected. In the present case, the first clinical sign was a swelling appearing over the upper part of the sternum twenty months before the death of the child, which subsided for five months and reappeared one month before she came under observation. This swelling fluctuated at one point and there was a suggestion of 'egg-shell crackling.' There was nothing in the clinical findings nor in the skiagraph to suggest an angioma, nor did the microscopical appearance at operation suggest anything other than a bone cyst, whilst the microscopical appearances of the fragments of bone removed at operation were inconclusive. Nevertheless, reviewing these sections with the advantage of a knowledge of the post-mortem data it is possible to find protruding from the bone marrow remnants of the lining endothelium of what were undoubtedly cavernous angiomatous spaces (fig. 24 and 25).

FIG. 24.—Sternum: cystic space below operation site.

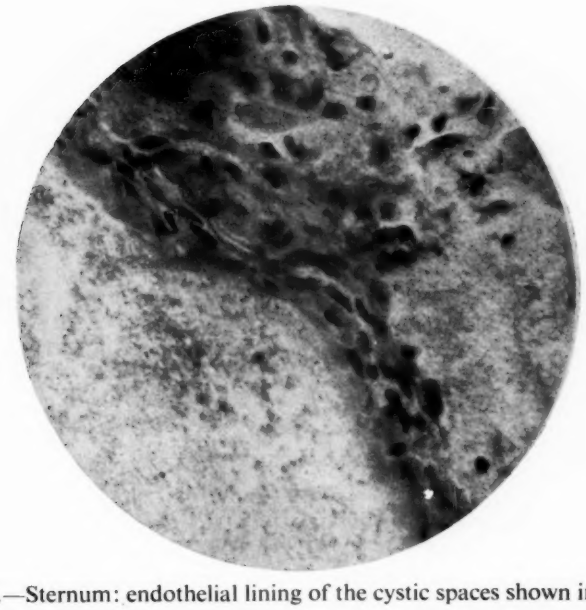

FIG. 25.—Sternum: endothelial lining of the cystic spaces shown in fig. 24.

In a study of the sections the kidney appears to be the most recently affected organ and here the spread of the angiomatous process into normal kidney tissue can be seen. This invasive tendency of the tumour is the only evidence of malignancy because individually the cells do not appear malignant; indeed, the striking characteristic of the tumour in every situation is the uniform and typical appearance of its cells which are long, spindle-shaped and fairly uniform in size with an oblong rather lightly staining single nucleus. There is no evidence of multinucleated giant cells nor of the spread of the tumour through or along the

walls of normal blood vessels. Examination of numerous portions of the organs which were available for histological examination does not suggest a secondary or metastatic growth arising from a primary focus; nowhere, in fact, does the structure vary from that of cavernous spaces lined by long endothelial cells, nor is there any suggestion of solid masses or bands of endothelial cells arranged in clumps or whorls to resemble an endothelioma.

In 1914, Shennan reported a remarkable case which in most respects is the counterpart of our own. This was a young woman, aged twenty-three years, who, when seventeen years old, developed a cough followed by anaemia, amenorrhoea and haemoptysis, the latter symptoms being due, it was thought, to a ' spongy ' throat. When she came under observation she was anaemic and the spleen was enlarged to three inches below the costal margin; there were no abnormal physical signs in the chest although blood was brought up by a slight cough. During the subsequent course of her illness the first acute symptom was pain in the left side and signs of an internal haemorrhage. Haemoptysis recurred and seemed to be related to her irregular menstruation. The anaemia was sometimes secondary in type but occasionally ' pernicious ' with a high colour index, variable poikilocytosis and a few erythroblasts. Purpuric spots appeared over the face, chest and arms, some of these being naevoid in appearance. One of the latter was removed from the buttock, but recurred and the histological sections showed dilated blood cavities, lined by endothelium. One year before death the upper part of the sternum and the inner end of the left clavicle became swollen and tender. During this time her general health improved but the spleen increased in size until it reached the crest of the ilium. Under treatment by x-rays the spleen became smaller and nodular; abdominal distension also occurred and repeated tappings were required, large quantities of bloody fluid being removed (e.g. 160 oz., 72 oz., 190 oz.) on different occasions. The patient died suddenly and at post-mortem multiple cavernous haemangiomata were found which involved the entire spleen, the thymus, the mediastinal lymph nodes, portions of the lungs, the liver, the bone marrow, kidneys, sternum, left clavicle and bodies of the lumbar vertebrae. Histologically these tumours were non-malignant, but locally they exhibited a certain invasive tendency. The nature of the tumour formation was thus described by Shennan: 'In its mode of extension and in its effects upon the tissue, it is undoubtedly malignant '; on the other hand, Hall (1935), in view of the fact that the foci were largely confined to the haemopoietic system and were all histologically benign, regarded the case as an example of ' multiple foci ' or ' system disease ' tumour.

From this description it is obvious how closely Shennan's and the present case resemble one another; moreover, the water-colour drawings, photographs and photomicrographs which illustrate his paper depict appearances so similar to those seen in the present case, that they can be regarded as examples of the same clinical syndrome. The similarities between the two cases may be thus classified.. First, the clinical histories have the following points in common: sex, duration, splenomegaly, anaemia, swelling of the upper part of the sternum and inner end of the clavicle, ascites and involvement of the lungs. Secondly, at autopsy the localization of the tumour masses were almost identical in each case, namely in the liver, spleen, mediastinum, thymus, kidneys, sacrum, clavicle and other bones. Thirdly, on histological examination of the tumours, the type of cell, the general structure, and the relation to normal tissues are extraordinarily alike in both cases. The only difference between the two patients is

that the liver in Shennan's case was not so extensively involved as in the present case.

Shennan's case is the only one discovered in the literature which is truly comparable with the one here reported, although it is not improbable that a case recorded by Grabowski (1927), under the title ' Angioma sarcomatodes systemisatum,' is a third example of this syndrome. Grabowski's paper was a thesis for the M.D. Degree of the University of Warsaw, and shortly before war broke out negotiations were in progress with the University of Warsaw for the loan of this thesis; now, alas, it is unavailable and it is even doubtful if the University Library exists. An abstract of the thesis in a German periodical, however, gives some details of the case.

The patient was a man aged thirty-two years who died seven months after the removal of an enlarged spleen. Microscopy of the organs showed a proliferation of the vascular endothelium, with a tendency to cavernous formation in the spleen, liver, bone marrow, lymph nodes, suprarenals and kidneys, and in the liver and spleen there was also sarcomatous proliferation of the endothelium. Since the endothelium of the blood-forming organs was affected and since all possible intermediate stages between the normal and pathological structures were found, the condition was considered to be ' a diffuse systematic affection of the endothelial part of the histiocytic apparatus.'

Etiological factors

It is now universally accepted that angiomata are due to a congenital developmental defect whereby vascular tissue is laid down which retains its embryonal characters and from which the angiomata grow independently. Virchow maintains that angiomata are caused by irritation of this embryonal tissue and Ewing (1928) states that ' cavernous angioma arise at any period of life—from congenital naevi—or in deep tissues, and they slowly enlarge by distension of the original vessels, and by formation of new vessels.' Foote (1919), however, believes that the disease arises in infancy from embryonic endothelium and that in adults it may arise from congenital naevi or from foetal inclusions which have remained dormant.

There are, however, certain other possible etiological factors. In a few instances the suggestion has been made that the tumours arise from a congenital naevus of the skin. In Shennan's patient cutaneous naevi were not present at the onset, but did appear later and were present for some time, one actually recurring after surgical removal. In the present case naevoid areas in the skin appeared shortly before death, although it is possible that they may have been present for a longer period in the deeper tissues of the skin; moreover, it is true that the swelling of the upper part of the sternum was an angioma which presented beneath the skin, but there is no evidence that this was the primary tumour. Borrmann (1907) reported the case of a woman aged twenty-six years who developed a simple angioma in the skin of the right breast which was removed surgically, and subsequently recurred several times; histologically all the recurrences were non-malignant and at autopsy many foci of similar structure were found in the lungs. Several other authors have reported cases of angiomata

in multiple organs associated with involvement of the skin, and those reported by Wollstein (1931), Bruchanow (1899), Orzechowski (1928), Schonberg (1923), Ewing (1928), Stamm (1891), Romdohr (1878), Ernst (1912) and von Falkowski (1914), show evidence that the skin may have had some significance in the origin of the tumour.

The possible relationship between portal cirrhosis and the origin of angiomata in the liver has been discussed by Ogilvie and Mackenzie (1936), who found five such instances in the literature and in addition five others in which the angiomata arose from the Küpffer cells in otherwise histologically normal livers, and three in which the tumours originated in the endothelium of the branches of the portal vein.

The question of the relation of specific congenital defects to the development of angiomata has also been raised by several writers; for instance, Hall (1935) in recording a case mentions a congenital anomaly in the right coronary artery which might have etiological significance, and Parker (1880), Orzechowski (1928), and Spiegal (1929) also considered the same point but without arriving at any definite conclusion.

From a study of the literature it appears that multiple haemangiomata are slightly more common in the female sex, this applying particularly to the ' system tumours.' The growth of the tumour and the relation of symptoms in Shennan's case seem to be related in some way to menstruation; Schlopsnies (1929) reported a case which followed childbirth, and the breast was the primary site in the cases described by Borrmann (1907), Ewing (1928), Robinson and Castleman (1936) and possibly Ross (1932).

Several authors produce considerable support for the theory that multiple haemangiomata have their origin in multiple foci; this view is held by Wollstein (1931), on the ground that the foci in her patient, although differing in size, were of the same age, and both Shennan's case and ours would certainly bear such an interpretation.

Grabowski, as already pointed out, believed that the tumours in his patient started in the endothelium of the reticulo-endothelial system, and both Pentman (1916) and von Falkowski (1914) describe instances of tumours arising in the endothelium of the blood vessels in a diffuse manner. Schlopsnies has, however, expressed the view that it is probably ' precarious to classify the angiosarcoma in Epstein's histiocytomatoses ' because angiosarcoma is a growth solely of the endothelium, and as will be seen in the following section, the endothelium of blood vessels cannot in the strictest sense be classified in the reticulo-endothelial system. In Schlopsnies' patient, already mentioned, the tumours were confined to the haematopoietic system. Paine (1931) has described a case of haemendothelioma of the spleen in which tumours were also present in the bone marrow and metastases in the liver; histologically this was a reticulum cell neoplasm, and was thought to be due to proliferation of neoplastic endothelial tissue in the haematopoietic system with certain resemblances to Hodgkin's disease. Gray (1929) maintains that although haemangiomata showing metastases are not necessarily confined to sites where reticulo-endothelial tissue is prominent, some are easily explained as an infection of the reticulo-endothelial system; he also cites a case recorded by Foot (1927) in which endothelial proliferation was present in the liver and other sites in the reticulo-endothelial system. Finally, Pentmann (1916) and Borissowa (1903) have

described tumours with multiple foci in the haematopoietic system which are not haemangiomata.

The reticulo-endothelioses

As a result of studies of patients presenting neoplasms involving several organs or parts of the body a controversy has arisen as to whether such conditions are due to generalized metastatic growths or to a generalized metaplasia and are examples of a system disease; also, if the latter, whether any of them can be regarded as diseases of the reticulo-endothelial system. There is no doubt that both Shennan's case and the present one—probably also Grabowski's—simulate closely many of the disease processes which have been classified as ' reticulo-endothelioses.' In this connexion two questions at once arise. First, can Aschoff's conception of a reticulo-endothelial system be accepted? Secondly, if the answer to the first question is in the affirmative, can a tumour arising from the endothelium of blood vessels be regarded as arising in part of that system? The term ' reticulo-endothelial system ' is in constant use in medical literature and certainly trips quite glibly off the tongue, but its definition is a much more difficult matter. Nevertheless, before the possible diseases of such a system can be discussed it is essential to have an idea of its constituent parts, although this is not rendered easier by the adoption of different names for the same cell, and by the fact that the very existence of the system is denied by some authorities.

ASCHOFF'S THEORY OF A RETICULO-ENDOTHELIAL SYSTEM. Certain cells of the connective tissue series have, in the living state, the property of becoming stained by weak solutions of certain colloidal dyes such as lithium carmine, pyrrole blue and trypan blue. This property is really one of phagocytosis and the degree of phagocytosis of a given cell is indicated by the intensity of the staining. Judging by this standard Aschoff (1924) classified these mesenchymal cells into six groups, of which those in the first four are in the ascending order of intensity of staining and the cells of the last two groups are derived from those of the third and fourth:

1. The endothelial cells of the blood and the lymph vessels which take the dye only when staining is carried to an advanced degree and then only in the form of fine granules.
2. Fibrocytic or ordinary fixed connective tissue cells. These take the dye after sufficiently prolonged staining and show fine granules.
3. The reticulum cells of the spleen and lymph glands.
4. The endothelial cells (called by Aschoff reticulo-endothelial cells) of the sinuses of the lymph glands, the blood sinuses of the spleen, Küpffer cells, the capillaries of the bone marrow, adrenal cortex and pituitary. The cells of this group, which were called littoral cells by Maximow to distinguish them from vascular endothelium, take the dye more intensely than any of the others.
5. The histiocytes (tissue histiocytes) or wandering cells of the connective tissue which are also found in the loose tissues of serous membranes, omentum and pleura. Other names suggested for these cells are macrophages (Metchnikoff), clasmatocytes (Ranvier), adventitial cells (Marchand), resting wandering cells and polyblasts (Maximow).
6. The pulp cells of the spleen (splenocytes), and the vitally staining monocytes of the blood (blood histiocytes). The latter arise from

the tissue histiocytes (group 5), splenocytes, and from the cells of groups 3 and 4 'which have been shed into the circulation or wandered into it.'

Aschoff combined groups 3 and 4 together and called them the reticulo-endothelial system because of their 'common function of producing reticulum and lining sinusoidal blood and lymph spaces . . . and because of the facility which these cells have of functioning simultaneously as lining endothelial cells and producers of reticulum.' In so far as the cells of groups 5 and 6 are derived from those of groups 3 and 4, they also form part of the reticulo-endothelial system; indeed Aschoff speaks of the cell groups 3 and 4 as forming the reticulo-endothelial system in the 'narrower sense,' and those of groups 3, 4, 5 and 6 as forming that system in the 'wider sense.' The cells of groups 3 and 4 have also been called stationary or fixed histiocytes and those of 5 and 6 wandering histiocytes. The term histiocyte simply means a tissue cell, but because of their active powers these (fixed and free) cells were called macrophages by Metchnikoff to distinguish them from the polymorphonuclear cells or microphages which do not stain intravitally. It has been suggested that certain other cells should be included in the reticulo-endothelial system of which, for the purpose of this paper, the most important are the reticulum cells of the thymus and glial cells of the brain. Aschoff does not accept this view and says 'they should not be included in the reticulo-endothelial system, the glial cells above all, because they do not participate at all in vital staining under ordinary conditions.' Nevertheless, del Rio-Hortega (1939) maintains that the microglia is derived from the mesoderm which grows into the brain with the blood vessels, and these cells, known also as 'mesoglia' or 'Hortega glial cells,' are now generally accepted as cells of the reticulo-endothelial system.

In addition to phagocytosis the cells of the reticulo-endothelial system have also other important functions in the metabolism of the body, as, for instance, the breakdown of the red blood cells, the formation of bile, the metabolism of fat and the production of antibodies.

The term 'reticulo-endotheliosis' is used by some writers to include proliferative changes in any of the components of the system, but by others it is restricted to conditions in which the change is supposed to arise in, and be more or less confined to, the cells of the fourth group, whereas the terms 'reticulosis' and 'histiocytosis' are applied to proliferation arising in and confined to the third and fifth groups respectively. Aschoff maintains that in all probability true neoplasms of the reticulo-endothelial system also occur, but that it is impossible to differentiate them from tumours of the ordinary vascular and lymphatic endothelium.

The question as to whether Aschoff is right in connecting up all the fixed and free cells which possess the power of phagocytosis and other important metabolic functions into a 'system' is one which has been the subject of considerable argument. For instance, Robb Smith (1937) criticizes the idea of a 'system,' but thinks it is possible to speak of reticulo-endothelial 'tissue.' Josephs (1937) also appears to prefer to speak of 'tissue' rather than a 'system,' for he defines 'reticulo-endotheliosis' as a group of diseases which at autopsy show widespread proliferation 'of a type of cell which is interpreted as arising from reticulo-endothelial tissue.' Jaffé (1938 a), in a masterly review of this subject, holds that the term reticulo-endothelial system has justified its existence, although he does not regard it as ideal since 'endothelial' obscures the distinction from vascular endothelium and 'reticular system' does not take into consideration the free and fixed wandering cells or the loose connective tissue and the histioid cells of the blood; nevertheless, 'a type of cell which is under continuous physiological stimulus deserves to be separated from the other mesenchymatous cells which lead a relatively quiet life.' In another article (1938 b) he says, 'the

differences between the reticulo-endothelial cells and the other cells are rather quantitative than qualitative,' yet in spite of this ' the reticulo-endothelial cells deserve to be regarded as a well defined cell system different from the other mesenchymatous cells, since, already under physiologic conditions, they are constantly in a stage of great functional activity, indicating that they play a very important rôle in the normal metabolism ' . . . and although ' the other mesenchymatous cells may eventually acquire similar properties, their response is sluggish as compared to that of the reticulo-endothelial cells, and hence of inferior biologic quality.' Dealing with the pathological changes in the reticulo-endothelial system, he states that, apart from malignant tumours which arise occasionally in the reticulo-endothelial cells of the blood-forming organs, such changes are, as a rule, reactive in nature and usually due either to infections or disturbances of metabolism; moreover, sometimes this reaction may be so marked as to give the impression of a primary disease. He points out that this impression of a primary disease is produced by a group of diseases, occurring particularly in children, which show a diffuse systematic hyperplasia of the reticulo-endothelial cells or of the reticulum cells only, and which in modern literature are called reticulo-endotheliosis or reticulosis respectively. Some French and Italian writers speak of the reticulo-histiocytic system in preference to the reticulo-endothelial system.

MAXIMOW'S THEORY OF THE PLURI-POTENTIALITY OF THE UNDIFFERENTIATED MESENCHYMAL CELL. Opposed to this conception, put forward by Aschoff, of a collection of cells related primarily by their physiological function, irrespective of their embryonic origin or histiogenic potentialities—in other words a physiological and not an anatomical system—there is the view enunciated by Maximow (1934) that these cells are unrelated functionally but related genetically to a common ancestral cell (the undifferentiated mesenchymal cell) which maintains its embryonic multipotency in postnatal life. According to Maximow the undifferentiated primitive mesenchymal cells, present in large numbers in the embryo, give rise in embryonic life to the connective tissue cells, the lymphocytes of lymphadenoid tissue, the blood-forming cells of the marrow, the blood cells and indeed all those cells which Aschoff includes in the reticulo-endothelial system. These undifferentiated mesenchymal cells have also been found by Maximow in the adult in the spleen, lymph nodes, liver, marrow and subcutaneous tissue, and form a syncytium in which it is difficult to define any cell boundary. In the unstimulated organ they are inconspicuous, and lie on the basement membrane of the lymph or blood sinuses; they do not store dyes nor produce reticular fibres and are non-mobile. On stimulation, however, they swell, develop a definite cell outline, their cytoplasm becomes denser, the nucleus smaller and richer in chromatin. They are then known as reticulum cells and form the sponge-like reticulum of the spleen, lymph nodes and bone marrow, in the interstitices of which lie the blood or lymph sinusoids. Reticulum cells are of two varieties, the littoral or sinus lining cell and the reticulum cell proper, to both of which reference has already been made (Hadfield and Garrod, 1938). Furthermore, according to Maximow, this undifferentiated mesenchymal cell syncytium can, under suitable circumstances, resume its embryonic character and give rise to the extraordinary variety of differentiated cells mentioned above.

RETICULO-ENDOTHELIOSIS OR RETICULOSIS? Accepting Maximow's thesis, Pullinger (1932) states that there exists a group of diseases of the reticulum ' in which proliferation is possible into one or several of the possible cell progeny ' and suggests that ' reticulosis ' (a term introduced by Letterer in 1924) is a more suitable name for these conditions than ' reticulo-endotheliosis,' and possesses the advantage that it allows the sub-division of the group in accordance with the predominant cell type. On the other hand, Abt and Denenholz (1936), who also accept Maximow's view, feel, as reported earlier in

the paper, that there is nothing to be obtained by calling a heterogeneous collection of cases ' reticulo-endotheliosis.' Hadfield and Garrod (1938) take up the standpoint that the views both of Aschoff and Maximow are correct; an attitude which they say receives strong support from a study of the reticuloses, under which title they class all those conditions ' in which there is generalized enlargement of the spleen, lymph nodes and liver due to hyperplasia of differentiated or undifferentiated mesenchymal cells.' Although Robb-Smith (1937, 1938) bases his classification on Maximow's doctrine, he also apparently accepts both views and his definition of reticulosis is a variant of those just quoted, being a ' progressive hyperplasia of reticular tissue with differentiations into one or more cell types,' and which is commonly systematized in that it affects throughout the body homologous tissue to that affected in the lymph nodes. He also points out that owing to proliferation arising at so many points ' infiltration ' may appear to be present, but stromal destruction does not occur and embolic dissemination is rare; moreover, free cellular elements may be present in the circulating blood (leukaemia). This definition accurately describes the present case with the sole exception that there were no abnormal cells in the blood.

Robb-Smith's classification of the reticuloses is an elaborate one, and its main sub-divisions are drawn from the three histological factors in the lymph glands: follicles, sinuses, and the reticular tissue of the rest of the gland (medulla). In follicular reticulosis there is hyperplasia of undifferentiated cells in the lymph follicles and malpighian bodies in the spleen and possibly the development of follicles in the periportal hepatic tissue and bone marrow. In sinus reticulosis (endotheliosis) there is hyperplasia of undifferentiated mesenchymal cells and littoral cells in the lymph sinuses, sinusoids of the liver and venous sinuses of the spleen and bone marrow, and in some cases a proliferation of tissue histiocytes. In medullary reticulosis there is hyperplasia of undifferentiated mesenchymal cells in the medullary tissue of the lymph nodes and the spleen, in the periportal tissue of the liver, the bone marrow, and possibly in the interstitial tissue throughout the body; the undifferentiated mesenchymal cells of the follicles and sinuses may also become involved. These three main subdivisions are further divided according to the predominant cell. The present discussion is, however, concerned only with the medullary reticuloses, which are divided into the following varieties: lymphoid (lymphoid leucosis), myeloid (myeloid leucosis and myeloid transformation), monocytic (monocytic leucosis), reticulum celled, storage reticulum-celled (lipoidosis, Gaucher's disease, Niemann-Pick's disease, xanthomatosis), histiocytic, pre-histiocytic fibrillary and fibro-myeloid (Hodgkin's disease).

In 1933 Siwe wrote an article having the title ' Die Reticulo-endotheliose—ein neues Krankheitsbild unter den Hepatosplenomegalien ' in which he reported one case and collected three others from the literature. In the paper by Abt and Denenholz, already referred to, these cases are further discussed, a new case described and four others collected from the literature. Included amongst the latter is a child who was a patient in the Birmingham Children's Hospital. This child was investigated there on several occasions and the details of his illness were recorded by the late R. J. Gittins (1933) in a paper on ' Anaemia and retiçulo-endotheliosis.' In view of the fact that Letterer described the first case of this type, Abt and Denenholz suggest that the condition should be called ' Letterer-Siwe's disease.' The symptomatology of this disease differs from that of the patient who is the subject of this paper in that all the children were under three years of age and that a haemorrhagic tendency chiefly manifested as petechiae or purpura was consistently noted, although it is perhaps noteworthy that as a terminal event small bluish tumours occurred in the skin of the present patient. Pathologically there was in every instance ' a widespread hyperplasia of non-lipoid storing macrophages in the liver, spleen, lymph

glands, bone marrow and lungs.' This condition has also been described under other titles, e.g., aleukaemic reticulosis (Letterer), acute reticulosis of infants (Oberling and Guérin, 1934), systemic endothelial hyperplasia of haemopoietic organs, and in Robb-Smith's classification it falls into the group of reticulum celled medullary reticulosis. The disease occurs in children between the ages of two and twenty-one months, runs an acute pyrexial course with generalized enlargement of the lymph nodes and splenomegaly, and terminates fatally in about six weeks. In the majority of cases there is a hypochromic anaemia and also a slight polymorphonuclear leucocytosis, although in others there is a lymphocytosis and neutropenia; frequently there is infection in the ears, nose and throat, and several cases have shown skeletal defects. Most writers regard this disorder as a systematized response to an infection. Indeed, Jaffé says ' reticulo-endotheliosis and reticulosis are septicaemias with an abnormal excessive response of the cells under discussion ' (1938 *b*). Although he also states in another contribution that the hyperplasia may be the ' morphological expression of an allergic tissue response to a septic infection ' (1938 *a*). Sacks (1938) thinks the term ' reticulo-endotheliosis ' should be limited to this class of case, which he describes as ' a systemic proliferation of the system of histiocytes unassociated with any demonstrable metabolic disturbance, and apparently occupying an intermediate position between inflammatory hyperplasia and malignant neoplasia.' Sacks divides systemic proliferation of the reticulo-endothelial system into three groups: (*a*) monocytic leukaemia, with or without local invasive neoplastic growth (Gittins and Hawksley, 1933); (*b*) retothelial (reticulum cell) sarcoma; (*c*) reticulo-endotheliosis.

The patient described by Gittins to whom Abt and Denenholz refer was one of a series of four children showing varying degrees of chronicity (acute to subchronic) of what we regarded and still do regard as erythronoclastic (haemolytic) anaemia. All these children at autopsy revealed marked histiocytic and reticulum cell reaction which we considered to be a reactive reticulosis or reactive reticulo-endotheliosis (Gittins, Josephs). Two of this series are regarded as examples of acute reticulosis by Robb-Smith, but he does not admit into that category the child claimed by Abt and Denenholz as suffering from Letterer-Siwe's disease. This child's illness showed the most chronic course of the series and at the autopsy there was found widespread reticular reaction with fibril formation replacing areas of haemopoietic tissue and thereby producing an aplastic anaemia. The diagnosis of a storage reticulosis such as Gaucher's disease was actually considered in this particular child because of the chronicity of the illness and the presence of anaemia and marked splenomegaly, but was ruled out of court by the degree of anaemia. As a matter of fact, neither this child nor the present case were ever considered to be in any sense suffering from the same or even allied diseases, although marked splenomegaly was present in both, because the outstanding condition in Gittins's case was the severe aplastic anaemia, the child only being kept alive by repeated transfusions; whereas in the present patient the outstanding feature was the enormous splenomegaly, the anaemia being but slight in degree.

It seems clear, then, that similar clinical symptoms may be produced by :

1. Generalized angiomatosis.
2. Retothelial sarcomatosis (reticulum cell sarcomatosis).
3. Storage reticulosis (storage reticulum cell medullary reticulosis).

4. Infection.
5. Reticulum celled medullary reticulosis (' hyperplasia of non-lipoid storing macrophages,' ' Letterer-Siwe's disease,' acute reticulosis of infants, aleukaemic reticulosis, reticulo-endotheliosis).
6. Hodgkin's disease.
7. Certain blood diseases, e.g., leukaemia and a form of erythronoclastic (haemolytic) anaemia.

As a matter of fact, in the present case after the suggestion of Hodgkin's disease was abandoned no other alternative diagnosis but that of a storage reticulosis was seriously considered.

Classification of angiomata

Whilst in the foregoing discussion the clinical and pathological evidence which supports the inclusion of the present case in the reticuloses (reticulo-endothelioses) has been given, yet both it and Shennan's and Grabowski's cases also find a place in the various suggested pathological classifications of the angiomata. For instance, Ewing (1928) distinguishes between ' multiple benign cavernous angiomas ' and ' metastasizing cavernous angiomas which exhibit certain peculiar features of malignancy,' and Dowd (1915) in reviewing thirteen cases of cavernous angiomata of the spleen divided them into multiple benign tumours in various organs and malignant angiomas with metastases. Ogilvie and Mackenzie (1936) describe two cases which they call malignant haemangio-endothelioma and suggest the groups ' malignant haemangio-endothelioma (with or without mestastases; histologically malignant) ' Schlopsnies (1929) on the other hand divides cavernous angiomata into ' system tumours ' and ' malignant metastasizing tumours.'

Multiple cavernous angiomata therefore appear to fall into three groups:

(*a*) Those occurring in the skin.
(*b*) Those occurring subcutaneously as benign growths in the various parts of the body where reticulo-endothelial tissue exists—system tumours.
(*c*) Those occurring in various parts of the body as a malignant metastasizing tumour.

The duration of multiple haemangiomata varies from a few weeks up to several years. The malignant metastasizing group appears to have the shortest course, while the ' system tumours ' usually survive much longer. Shennan's case was under observation for four years and our patient was first seen twenty months before her death.

Summary

A clinical and pathological report is given of a fourteen-year-old girl who showed clinical evidence of the ' osseous form of Gaucher's disease' but who at post-mortem examination was found to have suffered from cavernous angiomata varying in size in the liver, spleen, retroperitoneal glands, thymus, mediastinum,

lungs, pleura, kidneys and most of the bones of the body. The case is a difficult one to classify because of the widespread involvement of reticulo-endothelial tissue, although histologically it is apparently an example of multiple haemangiomata, the cells of which have benign histological characters. A discussion of the relation of this condition to ' reticulosis ' and ' reticulo-endotheliosis ' is included.

Thanks are due to Dr. C. G. Teall and the staff of the X-ray Department for many radiographic examinations, to Prof. Haswell Wilson for his help with the histological sections, to Dr. E. M. Hickmans for the biochemical estimations, to Mr. E. B. Brain for photographs, and to the Medical Research Council for defraying the expenses of the investigations.

References

Abt, A. F., and Bloom, W. (1928). *J. Amer. med. Ass.*, **90,** 2.
——— and Denenholz, E. J. (1936). *Amer. J. Dis. Child.*, **51,** 499.
Aschoff, L. (1924). *Lectures on Pathology*, New York.
Borissowa, A. (1903). *Virchows Arch.*, **172,** 108.
Borrmann, R. (1907). *Beitr. path. Anat.*, **40,** 372.
Brill, N. E., and Mandelbaum, F. S. (1913). *Amer. J. med. Sci.*, **146,** 863.
Bruchanow, N. (1899). *Z. Kinderheilk.*, **20,** 131.
Castle, W. B., and Minot, G. R. (1936). *Pathology, Physiology and Clinical Description of the Anæmias*, New York.
van Creveld, S., and Ter Poorten, F. H. (1935). *Arch. Dis. Childh.*, **10,** 125.
Dowd, C. M. (1915). *Ann. Surg.*, **66,** 177.
Erickson, B. N., Williams, H. H., Hummell, F. C., and Macy, I. G. (1937). *J. biol. Chem.*, **118,** 15.
Ernst, P. (1912). Quoted by Schlopsnies.
Ewing, J. (1928). *Neoplastic diseases*, third edition, Philadelphia.
Foot, N. C. (1927). *Amer. J. Path.*, **3,** 653.
Foote, J. (1919). *J. Amer. med. Ass.*, **73,** 1042.
Gittins, R. J. (1933). *Arch. Dis. Childh.*, **8,** 375.
——, and Hawksley, J. C. (1933). *Loc. cit.*, 241.
Grabowski, W. (1927). *Abstract in Zbl. allg. Path. path. Anat.* (1928–1929), **44,** 65.
Gray, J. (1929). *J. Path. Bact.*, **32,** 337.
Hadfield, G., and Garrod, L. P. (1938). *Recent advances in Pathology*, third edition, London.
Hall, E. M. (1935). *Amer. J. Path.*, **11,** 343.
Jaffé, R. H. (1938a). *Handbook of Haematology*, ed. by H. Downey, Minneapolis.
—— (1938b). *Practice of Pediatrics*. Edited by J. Brenneman, Hagerstown, Md. 1938.
Josephs, H. W. (1937). *J. Pediat.*, **11,** 607.
Letterer, E. (1924). *Frankfurt Z. Path.*, **30,** 377.
Maximow, A., and Bloom, W. (1934). *A Textbook of Histology*, second edition, Philadelphia.
Oberling, C., and Guérin, M. (1934). *Sang*, **8,** 892.
Ogilvie, R. F., and Mackenzie, J. (1936). *J. Path. Bact.*, **43,** 143.
Orzechowski, G. (1928). *Virchows Arch.*, **267,** 63.
Pachman, D. J. (1938). *Amer. J. Dis. Child.*, **56,** 248.
Paine, C. G. (1931). *J. Path. Bact.*, **34,** 139.
Parker, R. W. (1880). *Trans. path. Soc. Lond.*, **31,** 290.
Pentmann, I. (1916). *Frankfurt Z. Path.*, **18,** 122.
Pick, L. (1933). *Amer. J. med. Sci.*, **185,** 453 and 601.
Pullinger, B. D. (1932). *Rose research on lymphadenoma*, Bristol.
del Rio-Hortega, P. (1939). *Lancet*, **1,** 1023.
Robb-Smith, A. H. T. (1937). *M. D. Thesis, London University.*

Robb-Smith, A. H. T. (1938). *J. Path. Bact.*, **47,** 457.
Robinson, J. M., and Castleman, B. (1936). *Ann. Surg.*, **104,** 453.
Romdohr, M. (1878). *Virchows Arch.*, **73,** 459.
Ross, J. M. (1932). *J. Path. Bact.*, **35,** 899.
Sacks, M. S. (1938). *Arch. Pathol.*, **26,** 676.
Schlopsnies, W. (1929). *Virchows Arch.*, **85,** 274.
Schonberg, S. (1923). *Frankfurt Z. Path.*, **29,** 77.
Shennan, T. (1914). *J. Path. Bact.*, **19,** 139.
Siwe, A. (1933). *Z. Kinderheilk.*, **55,** 212.
Spiegal, H. A. (1929). *Arch. Pediat.*, **46,** 188.
Stamm, C. (1891). Quoted by Wollstein.
Virchow. Quoted by Ewing.
von Falkowski, A. (1914). *Beitr. path. Anat.*, **57,** 385.
Wollstein, M. (1931). *Arch. Pathol.*, **12,** 562.

STERNAL MARROW PUNCTURE IN CHILDREN

BY

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In certain blood dyscrasias the peripheral blood gives a poor indication of the pathological changes in the bone marrow, and a study of the actual nature and condition of the marrow is essential in establishing the final diagnosis of the disease. The choice of the sternum for this procedure sounds logical owing to its superficial location, the thin anterior lamina over the marrow cavity and its lifelong activity.

It is only during the past thirty years that bone marrow has been employed during life as a means of diagnosis. Ghedini in 1908, choosing the tibia as the site for biopsy, selected patients with latent malaria and leishmaniasis, and observed that the parasites were present in the bone marrow but absent from the peripheral blood. This method was, however, of no value in demonstrating the changes in the bone marrow of older children and adults, since the tibial marrow is only active from birth until the age of seven years, at which age it begins to undergo fatty metamorphosis, so that by the age of fifteen it is completely inactive. Seyfarth (1923) selected the sternum in place of the tibia for marrow biopsy, but still used trepanning, which being a surgical procedure was not suitable for routine clinical use. In 1929 Arinkin introduced the aspiration method for obtaining sternal marrow, and in 1937 Kato, dealing exclusively with infants and children, attempted to establish the normal picture of bone marrow at various ages. In 1939 Vogel and Bassen reported their observations on the marrow of a group of normal infants and children and on an unselected group with blood dyscrasia and other diseases.

Developmental anatomy of the human sternum

A post-mortem study, including radiological examination, of a series of sterna at various ages, including those of six and seven months foetuses, was undertaken to determine the developmental stages of the human sternum and to find out the correct depth to which the needle should be plunged to reach the marrow lacunae. The conclusions arrived at may be summarized as follows:

1. The ossification centres of the sternum, which correspond to the red marrow, appear at the sixth month of intra-uterine life, first in the manubrium, then in the other sternebrae.
2. Two stages of development of ossification centres have been noted. In the first, that of ' pairing,' one centre appears on either side of the middle line. At birth those of the manubrium are fused into one

large centre, while the next three segments contain small paired centres which are separate from each other.

3. In the second stage the paired centres in each segment fuse into one larger one, a process usually completed between the sixth and tenth years, when each sternebra becomes almost completely filled with its ossification centre corresponding to the bone-marrow content. In the lower segment of the sternum, however, pairing may persist as late as the twelfth year (fig. 1).

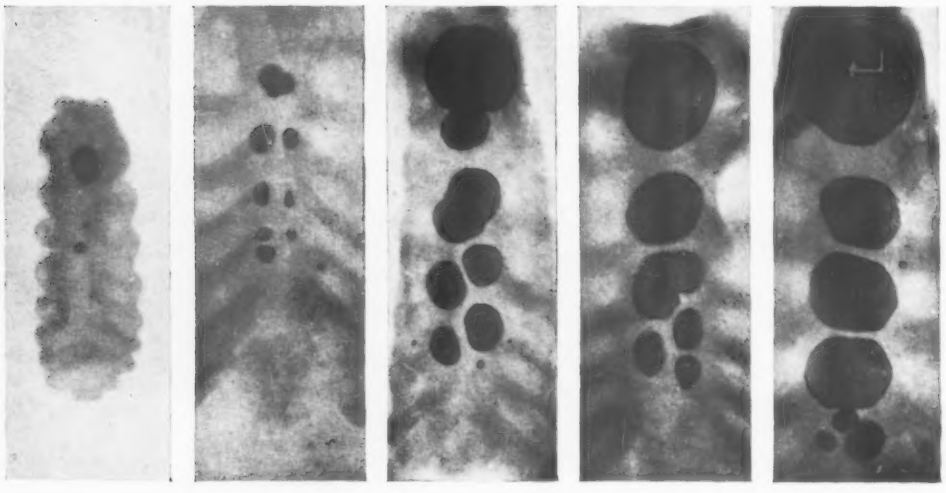

FIG. 1.—Skiagrams of human sterna to demonstrate the stages of development of the ossification centres.

I: Sternum of a six months foetus. II: Sternum of an infant eighteen days old. III: Sternum of an infant eight months old. IV: Sternum of an infant ten months old. V: Sternum of an infant fifteen months old.

4. The entire sternum is enclosed in a firm periosteal covering, the perforation of which is painful, making it advisable to anaesthetize this tissue by injecting some novocain subperiosteally when performing the sternal puncture.
5. The cartilaginous partitions between the sternebrae explain the failure of sternal puncture performed opposite a rib. It should be done opposite an interspace, otherwise the needle will hit against cartilage.
6. In the adult, however, the partitions in the body of the sternum are absent, and the marrow forms one continuous lake, and is equally accessible opposite the ribs and interspaces. The ossification centre of the xiphisternum, which is absent in children, starts to appear in adult life (fig. 2).

Technique of sternal puncture

General considerations

1. The centres of the manubrium and first sternebra are the earliest to appear; they fuse and attain a moderate size as early as the sixth month of life, and so appear more suitable than the other segments of the sternum for

FIG. 2.—Longitudinal sections to demonstrate the anatomical differences between the sternum of a child (left) and that of an adult (right).

performing the sternal puncture. Puncturing the manubrium, however, is not free from risk owing to the big vessels that lie behind, and so the centre opposite the second intercostal space appears the most suitable for this purpose in children. In the first few months of life this centre may be poorly developed and the puncture has to be made in the manubrium.

2. The anterior lamina of the sternum is cartilaginous in infants and young children, and gets gradually ossified in later childhood and adult life. In the case of the bony anterior lamina, a sense of resistance is experienced while performing the puncture, which suddenly disappears when the needle enters the marrow cavity. If the anterior lamina is still cartilaginous it is very difficult to know when one has reached the marrow through the soft cartilage, as in this case there is neither resistance nor a sense of 'giving way'; it is therefore necessary to be careful as regards the depth the needle has to attain in order to reach the marrow cavity, since otherwise there is the possibility of forcing the needle too deeply into the mediastinal space.

3. The total thickness of the sternum is composed of the anterior and posterior laminae and the marrow space between them. The dimensions at

the level of the second interspace in the children of our series whose ages varied from a few days to ten years were as follows:

	MINIMUM	MAXIMUM
Total thickness of the sternum	4·5 mm.	7·5 mm.
Thickness of anterior lamina	1 mm.	1·5 mm.
Marrow cavity	3 mm.	5 mm.
Thickness of posterior lamina	0·5 mm.	1 mm.
Thickness of skin and subcutaneous tissue over sternum	average 3 mm.	

Thus a distance of 0·5–0·8 cm. is the average through which the needle has to pass in order to enter the marrow space.

The operation

The needle used in the cases recorded here was the one devised by Dr. Salah of the Research Institute of Cairo, and consists of an ordinary lumbar puncture needle cut short and fitted with a movable shield which can be fixed at any required distance to limit the depth of penetration (fig. 3).

FIG. 3.—The sternal puncture needle.

The skin is first cleaned and disinfected with tincture of iodine, and some novocain is injected subcutaneously over the middle of the sternum opposite the second interspace. The shield is fitted at 0·5–0·8 cm. from the point of the needle, according to the age of the patient, the thickness of the sternum and the amount of the subcutaneous fat. The marrow cavity opposite the second intercostal space is readily located between the second and third ribs just below the prominent sterno-manubrial ridge. The needle with the stilette in place is inserted carefully. Because the suction necessary for aspirating the marrow must be fairly strong, a 10-c.c. syringe is used, even though a small amount of marrow fluid (from 0·1 to 0·2 c.c.) is all that is needed for morphological study. Aspiration of larger quantities in infants and children is inadvisable, since the marrow cavities are too small to permit the removal of material in large quantities. Besides, aspiration of large amounts of marrow would mean admixture

with it of the peripheral blood circulating in the medullary sinuses. In fact, when as much as 2 c.c. of material are removed, they consist almost exclusively of blood, and even when a few drops only are aspirated the material obtained consists of bone marrow mixed with blood.

The only time the patient experiences any pain or discomfort is during the aspiration of the marrow, and the larger the quantity aspirated the more marked is the pain, which is often described as a sensation of suction. This pain is a sure sign that the needle is right in.

A collodion dressing is applied to the site of the puncture, which heals quickly. Films are prepared, dried quickly and stained by Giemsa or May-Grunwald-Giemsa method. A total nucleated cell count can also be determined. At least 500 cells are counted and recorded in terms of percentage of the total number of the nucleated elements including the cells of the erythrogenic series.

Marrow of normal subjects

The criteria of normal bone marrow in infants and children have not yet been adequately determined. The principal published works are those of Kato (1937), Vogel and Bassen (1939) and of Tecilazic (1935). Kato's observations on fifty-one normal infants and children between the ages of one month and thirteen years revealed certain differences from the sternal marrow in adults. These differences are: (1) the relatively high percentage of the erythrogenic and lymphoid elements; (2) the relatively low percentage of the myeloid elements due to a lack of more mature granulocytes; the myelocytes and to a lesser degree the metamyelocytes forming the highest percentage of the myeloid elements, whereas the fully mature segmented forms are relatively few in number, being present to the extent of less than 7 per cent. This reversal of the percentage in erythrogenic and myeloid elements explained the low myeloid-erythroid ratio of 1 to 2 for infants and young children below four years, older subjects having a value of 3 to 4. The nucleated red cells ranged between 18 and 26 per cent.

Vogel and Bassen reported their observations on forty-one children. The rate of the myeloid to the erythroid cells was approximately 3 to 1. The myeloid cells showed a marked variation in different cases and the segmented neutrophils showed a higher percentage than in Kato's series, 6 to 34 per cent. as compared with 4 to 7 per cent. Tecilazic, working with tibial marrow of normal new-born children, found a marked predominance of the erythroid elements (70 per cent.) in the early days of life. This excess is apt to diminish during the second week of life to about 45 per cent. From then on the tendency is towards diminution of the erythroid elements until about the age of two years, when the figures are likely to approach those for adults. In Kato's series the erythroid elements ranged between 18 and 26 per cent., and showed practically no variations in the different age groups.

In the present series the number of normal cases examined was small. Fifteen cases in all, five infants from one year three months to two years old, and ten children from three years six months to five years five months old have been investigated. The result of the differential and total counts are detailed in tables 1 and 2. Preliminary blood and clinical examinations were relied upon to exclude any pathological conditions that might influence the marrow

TABLE 1

DETAILS OF THE TOTAL AND DIFFERENTIAL COUNTS OF MARROW SMEARS FROM TEN NORMAL CHILDREN

CASE	AGE		SEX	TOTAL COUNT	MYELO BLAST	NEUTROPHIL					EOSINOPHIL				BASO-PHIL	MONO-CYTES	LYMPHO-CYTES	ERYTHRO BLASTS	NORMO BLASTS	MYELOID ERYTH-ROID RATIO
	YEARS	MONTHS				PRE-MYEL.	MYEL.	META.	STAFF	SEGM.	MYEL.	META.	STAFF	SEGM.						
1. K. R. O.	4	7	Male	96,000	0·75	0·5	16·25	20·5	13	8	7·5	2	—	0·5	—	—	15	8	8	4·25
2. R. A. R.	4		Male	82,000	2	—	25	28	4	7·5	2·25	—	—	0·75	—	—	12	13·5	5	4
3. M. S. ..	5	5	Male	76,000	0·25	—	11	24·5	10	16	2·5	2	—	4	—	—	16	6	7	5·5
4. M. S. ..	4	4	Male	140,000	0·25	—	13	22	13	17	4	—	—	2·5	—	0·4	20	3·75	4	9
5. A. G. ..	5	5	Male	120,000	2	0·25	13	16	9	15	1·5	2·5	—	9	—	—	20·5	9	2·5	5·5
6. N. E. ..	4		Female	96,000	1·5	—	9	22	14	10	5	0·5	—	2·5	—	3	22·5	7·5	2·5	6·75
7. F. A. ..	4	3	Male	75,000	—	0·5	26	24	19	4	2	0·25	0·25	0·75	—	0·75	16·5	3	2	13
8. A. R. ..	4		Male	160,000	0·75	0·25	7·5	17	16	12·5	5	3	—	1·25	—	—	22·25	11	3·5	4·2
9. S. A. ..	3	6	Male	150,000	0·75	1·25	26	13·5	12	7	1·5	—	—	—	1	—	27	5·5	4	6
10. M. A. ..	4		Male	120,000	0·50	2	24	15·5	10	8	2·5	—	—	1·5	—	—	27	6	4	6

TABLE 2

DETAILS OF THE NUCLEATED AND DIFFERENTIAL COUNTS OF MARROW SMEARS FROM FIVE NORMAL INFANTS

CASE	AGE		SEX	TOTAL COUNT	MYELO BLAST	NEUTROPHIL					EOSINOPHIL				MONO-CYTES	LYMPHO-CYTES	ERYTHRO BLASTS	NORMO BLASTS	MYELOID ERYTH-ROID RATIO
	YEARS	MONTHS				PRE-MYEL.	MYEL.	META.	STAFF	SEGM.	MYEL.	META.	STAFF	SEGM.					
1. M. G.	1	10	Male	280,000	1·25	0·5	23	15	3	8·75	1·5	0·25	—	—	—	37·5	4·25	5·5	5
2. S. A.	1	3	Male	700,000	2	0·25	16	11·5	8·5	1·5	8	0·75	—	1·25	—	31·25	16·25	9	2·5
3. N. G.	2		Female	500,000	1·25	1·25	23·75	21·5	6·5	2·75	2·5	0·25	—	1	0·25	22·75	12·75	3·5	3·75
4. Y. F.	1	10	Male	309,000	1	2	15	19	6·5	13·5	4	2	—	1	—	13·5	15	7·5	3
5. R. M.	2	3	Male	300,000	2·5	0·25	7·5	16	7·5	8·5	1	0·5	—	—	—	33·5	16·5	6·5	2

picture. In the children of the series the findings could be summarized as follows:

1. The total nucleated cell count varied from 75,000 to 160,000 per c.mm.
2. There was a definite predominance of the myeloid elements. The myeloid-erythroid ratio was 4 to 6, and in two cases it was 9 and 13 respectively (cases 4 and 7). The percentage of the neutrophil segmented forms was generally low. In six out of the ten cases it was below 10, and in the rest of the cases it was about 15. The myelocytes, metamyelocytes and to a lesser degree the staff forms form the greatest percentage of the myeloid elements. In Kato's series the fully mature segmented forms were few in number, being less than 7 per cent.
3. The percentage of eosinophils was high. In five cases it ranged between 4 and 9, and in two cases it was 10 and 13 respectively.
4. The relatively high percentage of lymphocytes in most of the cases was striking.
5. The cells of the red series display a great variation from 5 to 18·5 per cent. In most of the cases the readings were lower than those of Kato in the same age groups (18 to 25 per cent.).

   The majority of the cells were erythroblasts. In Kato's series the cells were mostly normoblasts. Megaloblasts were absent in all the cases. Early erythroblasts in mitosis were frequently seen.
6. The myeloblasts averaged only from 0·25 to 2 per cent.
7. Megakaryocytes were invariably present.

In the infants of the series (between one and two years) the following differences from the older children were noted: (1) the total nucleated count was definitely higher, varying from 300,000 to 700,000 per c.mm.; (2) the percentage of lymphocytes was generally higher: in three cases it was above 30 and in one case it reached up to 37·5 per cent.; (3) the percentage of neutrophil segmented forms reached a lower level: in four out of five cases it was below 10 and in one case it was only 1·5 per cent. (table 2).

Bone marrow in certain pathological conditions

ANKYLOSTOMA ANAEMIA. The examination of the bone marrow of ten cases of ankylostoma anaemia revealed definite changes in its morbid anatomy. In nine out of the ten cases the marrow showed a marked degree of hyperplasia which was essentially erythroblastic and normoblastic. The total nucleated cell count in the marrow was generally between 250,000 and 300,000 per c.mm., but in two cases it was 1,120,000 and 2,790,000 respectively, thus indicating intense hyperplasia. The cytoplasm of the nucleated red cells was commonly basophilic or polychromatic, and numerous mitotic figures were seen in almost every case. Eosinophils were invariably present (fig. 7). This picture indicates an intense bone marrow stimulation similar to that obtained in post-haemorrhagic anaemias and favours the view that ankylostoma anaemia is due to chronic

bleeding. In one case the eosinophilic reaction was striking (22·2 per cent.) and was the main feature, the erythro-normoblastic reaction being slight.

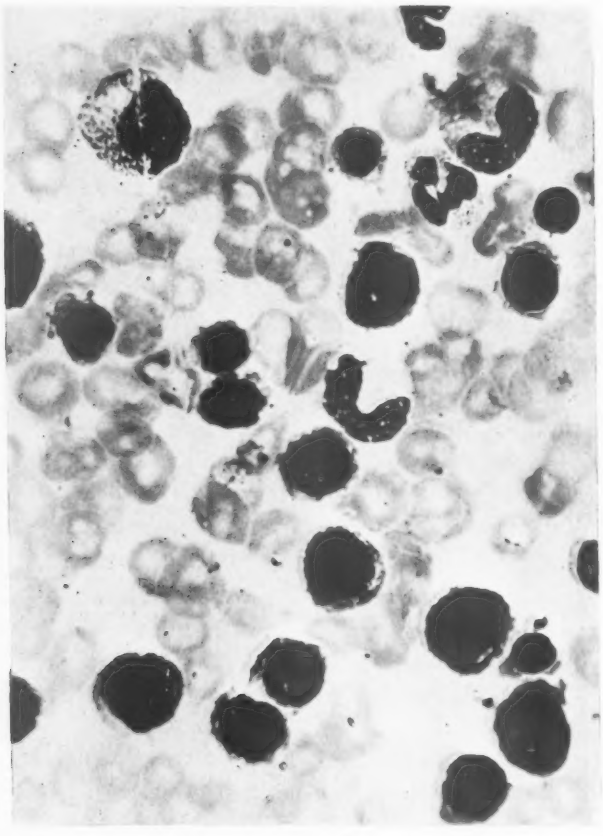

FIG. 4.—A microphotograph of the marrow of a case of ankylostoma anaemia. Note increase in the number of erythroblasts and normoblasts.

The findings of the sternal puncture may indicate a strong suspicion of ankylostoma infestation, though stools may at first be reported negative and repeated examination may ultimately demonstrate ankylostoma ova, as the following two cases show:

Case 1. A. M., a boy six years old, was admitted for pellagra and severe anaemia. First examination of the stools revealed no ankylostoma ova. As sternal puncture showed an erythro-normoblastic reaction (37 per cent.), stools were re-examined and on the third occasion ankylostoma ova were found.

Case 2. S. M. E., a girl eleven years old, in whom the first examination of the stools revealed only ascaris ova, had on sternal puncture a marked erythro-normoblastic reaction (43 per cent.). The stools were re-examined and ankylostoma ova were detected at the fourth attempt.

EFFECT OF IRON THERAPY. The administration of iron produces a gradual diminution of the general cellularity, and at the same time maturation is stimulated. The nucleated red cells gradually return to their normal level, and

when iron therapy is completed, the bone marrow resumes its normal character, as exemplified by the record of the following case:

Case 3. A. M. E., a boy of twelve years of age, was admitted for pellagra, progressive wasting and pallor. Examination of the stools revealed ankylostoma ova. Blood examination showed 30 per cent. haemoglobin, red blood cells 2,634,000 per c.mm. and eosinophils 10 per cent. Sternal puncture revealed a definite erythro-normoblastic reaction (40·5 per cent.). Carbon tetrachloride was given as an anthelminthic. Iron was given for a month, after which another sternal puncture was done. It revealed a diminution of the general cellularity, and the erythroblasts and the normoblasts approached the normal figure (22·5), and the myeloid-erythroid ratio rose from 1·5 to 4·3.

The presence of a mixed ascaris and ankylostoma infestation does not seem to alter the characteristic bone marrow picture of ankylostoma anaemia. The marrow of cases with pure ascaris infestation was examined and no characteristic picture was revealed.

BILHARZIASIS. The bone marrow of five cases of urinary bilharziasis was examined. Four cases showed a moderate eosinophilic reaction ranging between 10 and 15. The fifth case, that of a child ten years old, revealed a high

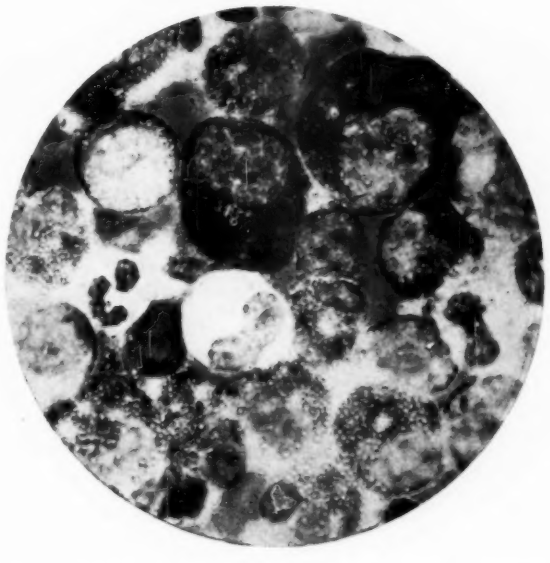

FIG. 5.—A microphotograph of the marrow of a case of urinary bilharziasis showing an intense eosinophilic reaction.

eosinophilia in the differential count of the peripheral blood (70 per cent.) and a study of the bone marrow showed an intense eosinophilic reaction of 60 per cent. (fig. 5).

CRETINISM. The sternal marrow of two cases of cretinism was examined. The main feature in the two cases was the low total count, indicating hypoplasia of the bone marrow. This depression is most probably the result of the general slowing down of metabolic and other processes of the body in hypo-thyroid states.

In one case, aged twelve years, the total nucleated cell count was 40,000 per c.mm., and rose after one month's thyroid treatment to 190,400. The differential count was as follows: neutrophil myelocytes 16, metamyelocytes 11, staff cells 18, segmented 20, eosinophils 2·4, monocytes 1·4, myeloblasts 0·4, lymphocytes 20·4, erythroblasts 6, normoblasts 5·2 per cent. The effect of thyroid on the general cellularity of the marrow was striking (fig. 6 and 7), and the nucleated red cells gave a higher figure of 15 per cent. The haemoglobin

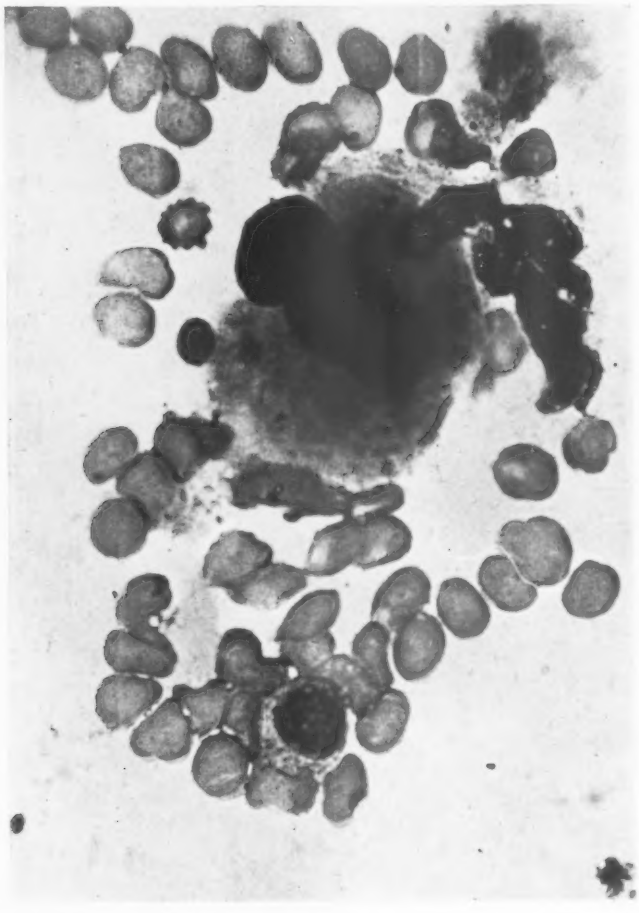

FIG. 6.—A microphotograph of the marrow of a case of cretinism before thyroid treatment. There are only one megakaryocyte and few nucleated cells.

in the peripheral blood rose at the same time from 30 to 60 per cent. at the end of the treatment.

In the second case, aged three years, the total nucleated cell count was 67,700 per c.mm. The differential count was as follows: myelocytes 18, metamyelocytes 20, staff cells 12, segmented 12, eosinophil 5·2, monocytes 0·4, lymphocytes 11, erythroblasts 13, normoblasts 8, punctate basophilia 0·4 per cent., myeloid-erythroid ratio 3·1.

Summary

1. A radiological and naked eye study of the human sternum was carried out to determine the developmental stages of the ossification centres and to know the correct depth to which the needle should be plunged in order to reach the marrow cavity.

2. The details of the technique of sternal puncture are discussed.

3. A study of the marrow of ten normal children from three years six months to five years five months old and five infants from one to two years old has been carried out.

4. The bone marrow picture in ankylostoma anaemia has been studied. An erythro-normoblastic reaction is the outstanding feature.

5. The results of examination of the marrow of two cases of cretinism and five cases of bilharziasis are reported.

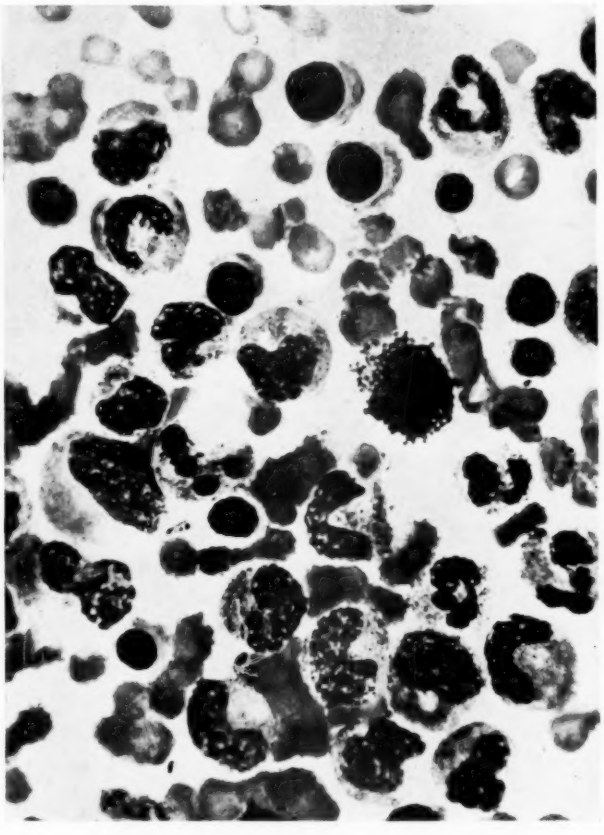

FIG. 7.—The same case as fig. 6 after one month's thyroid treatment. There is a definite bone marrow stimulation.

References

Arinkin, M. J. (1927). *Vestn. Khir.*, **10,** 57.
—— (1929). *Folia haemat., Lpz.*, **38,** 233.
Ghedini, G. (1908). *Clin. med. ital.*, **47,** 724.
Kato, K. (1937). *Amer. J. Dis. Child.*, **54,** 209.
Salah, M. (1934). *J. Egypt. med. Ass.*, **17,** 846.
Seyfarth, C. (1923). *Dtsch. med. Wschr.*, **49,** 180.
Tecilazic, F. (1935). *Pediatria*, **43,** 658.
Vogel, P., and Bassen, F. A. (1939). *Amer. J. Dis. Child.*, **57,** 245.

A SIMPLE SPECIFIC PRECIPITATION TEST FOR COW'S MILK

BY

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In recent years it has become a practical possibility to distinguish between various types of milk. The difficulty of providing children's hospitals with a sufficient supply of breast milk from wet-nurses has made it necessary to try to collect mother's milk either by voluntary contribution or by purchase. Thanks to successful collaboration with the local welfare centres, the Gothenburg Children's Hospital has succeeded in obtaining the required quantity of breast milk from mothers who have an ample supply of milk or from mothers who have already weaned their babies or are about to do so. In 1938, the Children's Hospital was thus able to purchase more than 300,000 c.c., three Swedish crowns per 1000 c.c. being paid for the milk. In the same way the welfare centres have succeeded in getting breast milk for special cases such as newborns and prematures, when for some reason the mother herself could not supply it. In several localities in Germany, France, Italy, and America, collection of mother's milk on a larger scale has been organized. In all these countries the necessity of controlling the contributed milk has arisen. A great deal of work has been devoted to trying to find a reliable method of detecting adulteration of breast milk by the addition of cow's milk. Both physico-chemical and biological methods have been used. The methods and reactions used in differentiation between cow's milk and breast milk are briefly reviewed.

Umikoff, in 1896, showed that after adding ammonia and heating to 60° C., breast milk turned a reddish-lilac colour, whilst cow's milk became yellow. According to Sieber the reaction depends on the lactose in combination with the citric acid present. The colour is influenced to a certain degree by the quantity of fat. Addition of cow's milk gives a weaker muddy grey colour, which clearly shows the difference when compared with pure breast milk from the same individual.

Tugendreich (1911) showed that on adding silver nitrate to breast milk and heating, the mixture assumed a brown or brownish-violet colour; whereas with cow's milk such a mixture remains colourless or has only a very faint colour. Commonly the reaction does not detect a moderate addition of cow's milk.

The neutral-red reaction of Moro (1912) is based on the different hydrogen-ion concentrations which exist in cow's milk and breast milk. The reaction of breast milk is more nearly neutral (about *p*H 7·0), cow's milk being more

acid, with a *p*H between 6·3 and 6·6. Cow's milk and old sour breast milk, on the addition of neutral-red, give a red colour, whilst fresh breast milk turns yellow. In spite of an addition of 10 per cent. cow's milk the colour remains yellow or light yellow-red.

Bauer's (1913) nile-blue reaction is also a test which, like Moro's reaction, depends on the different hydrogen-ion concentrations. If a drop of 0·25 per cent. solution of nile-blue sulphate is added to a test-tube half-filled with ether which is then shaken and to which one to two c.c. milk are then added, the cow's milk after vigorous shaking sinks to the bottom and is blue-coloured, whilst fresh breast milk remains white. The colour disappears in a slightly acid aqueous solution, but persists in the ether in a neutral or alkaline reaction. Breast milk, when kept at room-temperature, becomes acid and gives a positive reaction. An addition of 25 to 30 per cent. of cow's milk to fresh breast milk is demonstrable by this reaction.

Edelstein (1921) used the relatively high lactose and low albumin content of breast milk to detect adulteration. From the tint which originates by a reduction of a copper salt solution by the lactose in the milk-serum, and by the amount of oxide of iron necessary for a quantitative precipitation of albumin, Edelstein was able to ascertain whether or not the mother's milk had been mixed with cow's milk or with water. An addition of 20 to 30 per cent. could thus be detected, but he did not consider this method always reliable.

Jacobi (1922) showed that on the addition of an equal quantity of concentrated sulphuric acid, breast milk turns brown, whilst cow's milk turns purple. Addition of cow's milk to the breast milk gives a darker brown colour. This difference in colour depends on a difference in the type of casein.

Zimmermann's method (1928) is based on the difference between the casein of breast milk and of cow's milk and the disparity in precipitation in the test-tube due to this difference. The milk is mixed with decinormal sulphuric acid, diluted with distilled water. The cow's milk casein is precipitated as clots, which settle at the bottom as a sediment. According to Urbach (1938) the result is best read after forty-eight hours. Negative and positive control is necessary ; that is, an absolutely pure specimen of breast milk has to be compared with milk from the same individual adulterated 10 per cent.

Kapeller and Gottfried (1920) described a method which was based on the capacity for refracting light by the so-called acetic milk-serum. After adding a certain quantity of acetic acid, heating and filtering, serum from breast milk has a considerably higher light-refraction than that from cow's milk. From the degree of reduction in the refraction of light, it is possible to demonstrate an addition of 20 per cent. cow's milk or 10 per cent. water, but an absolutely reliable control from the same individual is necessary as a comparison.

Kayser (1927) pointed out that breast milk in ultra-violet light showed a bluish-violet fluorescence, and that cow's milk, on the contrary, gave a yellow one. Sometimes breast milk could also give a yellow fluorescence and later on Kayser (1937a, b) has pointed out that eating liver produces exactly the same yellow fluorescence, probably depending on the presence of lactoflavin in the milk.

According to Grossfeld (1935) it would be possible to distinguish between breast milk and cow's milk by analysing the fat. The so-called butyric-acid-fraction, which is an expression of the proportion of the lower fatty acids, butyric acid, and capric acid, is considerably less in the fat of breast milk than in the fat of buttermilk. The method could certainly be used, but is much too complicated to be practical.

The biological methods for distinguishing between the various kinds of milk are the precipitation reaction, the complement fixation reaction, and the anaphylactic test. From a practical point of view, the anaphylactic test is

unavailable. Even the complement fixation test is too complicated, virtually requiring a special laboratory, but it is according to Bauer (1913, 1930) a distinct and specific reaction. Bordet, in 1899, was the first to show that if milk was injected into rabbits, precipitins were formed in the serum. It appeared that this reaction was not strictly specific, as it also gave positive reactions with the milk of nearly related animals. The test-serum from the cow also precipitates, for instance, goat's milk, though not in the same degree as the homologous milk. According to the researches of Hamburger, Schlossmann, Moro, and others, it is not only casein but also lactalbumin and lactglobulin which produce antibodies, though it is first and foremost the casein, which in the precipitation test gives the most evident reaction. The casein in itself is not a homogeneous product. Svedberg and Carpenter (1930, 1931) have been able to distinguish by the determination of the molecular weights three different fractions with molecular weights of 75,000 to 100,000 ; 188,000 ; and 375,000, which also remained distinct from a serological point of view (Carpenter and Hucker, 1930). The casein of breast milk and cow's milk differs in its chemical composition ; breast milk contains, amongst other things, a higher percentage of sulphur. There is no serological relationship, and a non-specific reaction is therefore not to be expected.

The precipitation reaction is, as is well known, carried out by carefully layering the solution which is to be examined, upon the specific precipitation serum. If positive, a slight precipitation disc forms at the junction of the solutions. In order to be able to distinguish this disc, which may be very small, both liquids must be as clear as possible. Although most of the fat is removed by vigorous centrifuging and the milk is highly diluted, it remains slightly milky. This makes the interpretation of the test impossible or very difficult. In these cases it is necessary to carry out the precipitation reaction more as an agglutination test. Dilutions of the milk to be examined are mixed with the specific serum. In a positive reaction the precipitate forms a sediment which sinks to the bottom of the test tube.

Jordanoff and Koschucharoff (1929) and Jordanoff (1932) in Sofia worked out a new serological method for differentiating different kinds of milk. This was the result of large scale attempts to distinguish between cow's, buffalo's, sheep's, or goat's milk. Most of the lactosera which they produced were non-specific and often precipitated all types of milk. They only succeeded in getting pure specific sera after having begun to saturate the serum in vitro with the other kinds of milk. Such purified serum is called lactotest. They suggested that the reaction should be performed on a slide (as in a slide agglutination reaction or in blood grouping), and that undiluted milk and undiluted serum should be used. This precipitation reaction carried out on a slide is an excellent method, and is easy to execute and to interpret. Thanks to the fact that undiluted milk is used, the precipitin titre of the serum need not be high. It is of course desirable that the serum is sufficiently strong for an obvious and unmistakable reaction to be obtained. As the caseins in breast milk and cow's milk are not closely connected, the lactoserum need not be saturated and freed from non-specific components.

Method

The preparation of precipitin serum. Usually for the production of antibodies, rabbits are given an intravenous injection of gradually increasing doses of antigen every fourth or fifth day. At the beginning of my experiments. I adopted this procedure. The result was not successful. Following even the third milk-injection, some rabbits suffered from severe anaphylactic reaction

and some actually died of anaphylactic shock. It was just those rabbits which showed an unusually good antibody-formation and consequently were especially suitable, which died of shock. By continuing my experiments and giving the rabbits a small desensitizing dose of 0·1 c.c. about half an hour before they got their regular injection, I succeeded in avoiding such mishaps. Recently I have adopted a different procedure. A certain number of rabbits were simultaneously injected five times intravenously with 5 c.c. milk on alternate days. The last injection was made with great care to avoid a possible anaphylactic shock. On the fourth day after the last injection the rabbits were bled and the sera generally showed a sufficient titre (1 : 20,000 or more). After having fasted one night, the rabbits were completely bled, in order to get the serum as clear and as fat-free as possible. As a preservative carbol was added to the serum to a concentration of 0·5 per cent.*

When testing the strength and suitability of a test serum, it is necessary, in addition to notifying the precipitation-titre, to do a preliminary slide precipitation test with breast milk containing varying amounts of cow's milk, for instance, 10 per cent., 5 per cent., 2 per cent., and 1 per cent. If there is a strong and rapid reaction with 10 per cent. and 5 per cent., and positive though weaker reactions with the lesser percentages of cow's milk, the serum should be considered suitable for the purpose.

Controls with pure breast milk must not, of course, give any reaction. The negative reactions like the weak positive ones, should be verified microscopically by slight magnification. When the serum gets old, the titre drops and before testing it should be controlled to see if it is still fit to be used. To keep the serum as long as possible, it must be put in an ice-box. Sometimes a deposit forms at the bottom of the bottle, and this has to be removed by centrifuging in order to avoid the risk of getting false positive reactions.

Performance of the test. A few cubic centimetres of the milk which has to be examined is centrifuged, and the fat which rises to the surface is removed. The small clots of fat which form when the milk is kept may simulate a positive reaction, at least to an inexperienced investigator. When small additions of cow's milk are to be detected this skimming of the milk is essential. Two or three platinum-loopfuls from the undiluted milk are put on the slide, after which one or two drops of test serum are added and stirred with a glass rod or the platinum needle. By slightly raising and rolling the slide, as in the examination of blood groups, the fluids are carefully mixed. When the reaction is positive, precipitates, which gather at the periphery of the drop, are formed immediately or within a few minutes. When the reaction is negative the fluid remains homogeneously turbid, and no flocculation occurs (fig. 1). Sometimes small lumps of fat are formed which appear in the middle of the test. With smaller additions of cow's milk the reaction may be difficult to interpret. Microscopically the flakes appear at the periphery (fig. 2), and can easily be distinguished from small masses of fat, if the fat of the milk has been almost all removed. Should there be too much fat in the milk the masses of fat adhere

* This method has successfully been used in other places, for instance, at the State Bacteriological Laboratory in Stockholm.

to the small precipitates, and in that case it may be difficult even microscopically to distinguish them from normal small masses of fat.

Boiling the milk does not alter the result of the reaction. Casein is a thermostabile albumin. If breast milk mixed with cow's milk is kept in an ice-chest, the presence of cow's milk can be proved even after several days. On the contrary, if the milk is kept at room temperature the test cannot be performed

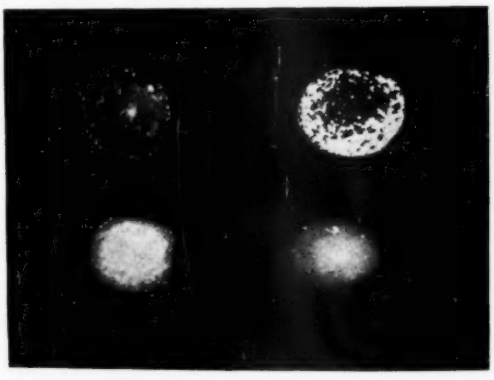

FIG. 1.—The slide precipitin test performed with cow's milk and with breast-milk containing 10 per cent., 3 per cent., and 0 per cent. of cow-milk.

as the milk goes sour. The casein separates and can no longer react with the specific serum. The diet of the mother has no effect on the reaction. Even when an increased quantity of cow's milk is taken, the method does not indicate

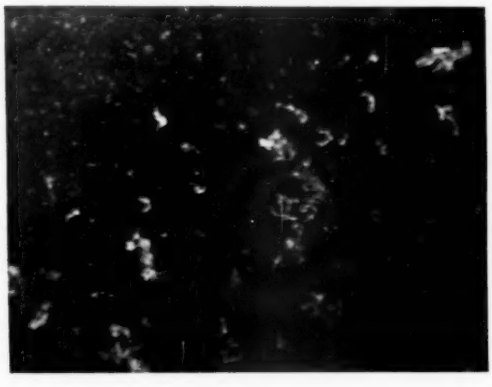

FIG. 2.—The reaction microscopically performed with 1 per cent. of cow's milk in breast-milk.

any adulteration of the breast milk (Urbach, 1938). This accords with Stuart's findings (1923) that albumin is not converted into milk and cannot be discovered in it, even after it has been taken in large amount.

Conclusion

This slide precipitation reaction is an excellent method for detecting admixtures of cow-milk with breast milk. Samples of breast milk from the same

individual are not needed as a control. The test is specific and not influenced by the food consumed ; it is easily performed and gives a definite result in a few minutes. It is unquestionably better and more reliable than earlier known methods.

References

Bauer, J. (1913). *Die Methodik der biologischen Milchuntersuchung, Stuttgart.*
—— (1930). *Handb. Milchwirtschaft*, **1,** 109.
Carpenter, D. C., and Hucker, G. J. (1930). *J. infect. Dis.*, **47,** 435.
Edelstein, F. (1921). *Z. Kinderheilk.*, **30,** 326.
Grossfeld, J. (1935). *Z. Untersuch. Lebensmittel*, **70,** 459.
Handbuch der Lebensmittelchemie, (1936), **3.**
Jacobi, W. (1922). *Mschr. Kinderheilk.*, **23,** 44.
Jordanoff, M. (1932). *Z. Fleisch- u. Milchhyg.*, **42,** 300.
————, and Koschucharoff (1929). *Jber. vet. Fak., Sofia*, 16.
Kapeller, G., and Gottfried, A. (1920). *Münch. med. Wschr.*, **67,** 813.
Kayser, M. E. (1927). *Ibid.*, **74,** 2142.
—— (1937a). *Dtsch. med. Wschr.*, **63,** 136.
—— (1937b). *Loc. cit.*, 712.
—— (1938a). *Ibid.*, **64,** 297.
—— (1938b). *Le lait*, 18.
Moro, E. (1912). *Münch. med. Wschr.*, **59,** 2553.
Stuart, H. C. (1923). *Amer. J. Dis. Child.*, **25,** 135.
Svedberg, T., Carpenter, L. M., and Carpenter, D. C. (1930). *J. Amer. chem. Soc.*, **52,** 701.
—— (1931). *Ibid.*, **53,** 1812.
Tugendreich, G. (1911). *Berl. klin. Wschr.*, **48,** 224.
Umikoff, N. (1896). *Jhrb. Kinderheilk.*, **42,** 356.
Urbach, H. (1938). *Klin. Wschr.*, **17,** 633.
Zimmermann, M. (1928). *Z. Kinderheilk.*, **45,** 310.

RHEUMATIC HEART DISEASE IN IDENTICAL TWINS

BY

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It has long been recognized that acute rheumatism and rheumatic heart disease occur more frequently in some families than in others. It is, however, far from clear whether this increased incidence is due to genetic factors or to exposure to the same environment.

Paul (1931) found that the spread of the disease through families suggested that the disease was due to an infection, in which the possible rôles of environment and of an inherited disposition were undetermined. Roberts and Thomson (1934) considered that the most reasonable explanation of the family incidence of the disease was that it is due to genetically determined differences in susceptibility, but that environmental factors are necessary for the disease to become manifest in susceptible individuals. Wilson and Schweitzer (1937) from a study of the familial incidence of the disease concluded that the factor of susceptibility to rheumatic fever might be inherited as a single autosomal recessive gene. Read, Ciocco and Taussig (1938) confirmed the high frequency with which rheumatic heart disease is found in parents and siblings of rheumatic children. They considered that although their study reveals a strong familial tendency to the disease, the findings were not sufficiently definite to determine the relative importance of heredity and environment. In view of this doubt the study of rheumatic heart disease in identical twins may be of value. Morgan and Webster (1938) have already reported mitral stenosis developing after rheumatic fever in identical twins, one of whom died at the age of twenty-three from the disease. Kaufmann and Scheerer (1938) amongst the records of 8500 twins found seventy-two sets in which acute rheumatism was recorded. Twenty-seven of these were uni-ovular, and both twins were recorded as having rheumatism in only five cases; of the forty-five binovular twins concordance was observed only once.

A pair of twins both of whom apparently developed rheumatic heart disease at the same time has recently been observed.

Case reports

Pamela and Patricia B. were born in December 1932. They weighed the same at birth and their mother states that she tells them apart by their voices. They have lived together all their lives and had measles and whooping-cough together and also occasional colds and sore throats. In May 1939 Pamela had a sore throat, developed a scarlatiniform eruption and was sent to a fever

hospital with scarlet fever. Following the scarlet fever she had no joint pains, but developed carditis and was in hospital for nine weeks. When first seen, fifteen weeks after the onset of the scarlet fever, her apex beat was diffuse and forcible in the fifth space in and beyond the mid-clavicular line. There was a loud systolic murmur at the apex. Patricia, who was examined at the same time, gave a history of tonsillitis when her sister had scarlet fever, but she developed no rash and was kept at home. She had no joint pains, but on examination her apex beat was diffuse and forcible in the fifth space in the mid-clavicular line and there was a loud apical systolic murmur. X-rays show that Pamela's heart had a more convex left border and was slightly larger than Patricia's.

Electrocardiograms are closely alike.

The evidence on which this pair is considered monozygotic is as follows:

Facial appearance similar—mother finds difficulty in distinguishing them. Hair and eye colour identical.

	PAMELA	PATRICIA
HEIGHT	119·5 cm.	120·5 cm.
WEIGHT	3 st. 8 lb.	3 st. 7 lb.
HEAD LENGTH	176 mm.	174 mm.
HEAD BREADTH ..	144 mm.	144 mm.
BLOOD GROUP	A_1MN (negative to Pig. V_7D)	A_1MN (negative to Pig. V_7D)*

FINGER-PRINTS. Right hand: first, second and third fingers similar according to Stocks' method. Left hand: first and third fingers similar. There is, in addition, a crossed similarity between Patricia's right little finger and Pamela's left. The number of resemblances between the right and left hands of the two children is four. Dr. Percy Stocks, to whom the finger-prints and other data were submitted, writes: 'I agree with your results for this pair, and from the finger-prints alone I should expect them to be dizygotic. The photographs and measurements seem to point to the other conclusion. I should feel doubtful about classing this pair as monozygotic.' In an attempt to settle this doubt X-rays of the twins' wrists, elbows, ankles and knees were made to see if there were any difference in the ossification of the epiphyses. All were identical with the exception that the pisiform bone was ossified in Pamela's left wrist but in neither of Patricia's, and that all Pamela's bones show a marked 'white line' near the end of the diaphysis, presumably the result of the scarlet fever.

Actually the number of resemblances in the finger-prints by no means rules out a diagnosis of monozygocity, as is clear from Dr. Stocks' papers (1930, 1933). In addition to the identical facial appearance the children also display remarkable resemblances in movements and mannerisms. In view of this, the measurements and the fact that the mother herself sometimes finds it easy to mistake them, it seems highly probable that the pair is in fact monozygotic.

This pair presents the picture of rheumatic carditis developing with no recognized arthritis in both children following what was almost certainly a throat infection with the same haemolytic streptococcus. One developed a rash and was subsequently treated differently from the other, yet both developed the same type of rheumatic attack and are left with a similar cardiac lesion. In this pair it would appear that given the necessary infection the development of acute rheumatism, and further the form which the attack took, was largely determined by genetic factors. At the same time, the response to the erythrogenic toxin produced by the infecting organism was clearly different in the two

* Pig. V_7D is a new blood group antibody being investigated by the Galton Laboratory.

patients, since one developed a well-marked rash and in the other any rash which occurred was so slight that it escaped notice.

The second pair of twins to be considered are Harry and Fred H., who were born in October 1929. Fred had chicken-pox as a baby, but Harry escaped although they slept together throughout the illness. They had measles in early childhood. At the age of five years and three months Harry had acute appendicitis and an ' enlarged inflamed appendix with a faecolith in the distal third ' was removed. Fred had his appendix removed when he was six years and two months old; it was described as ' long and kinked ' and contained a faecolith. The boys had been together all their lives except for these two illnesses. In August 1938 Harry was admitted to the Children's Hospital under the care of Dr. N. L. Price, to whom I am indebted for the following particulars. He was taken ill on August 3 with pain and swelling in the knees, later the ankles, elbows and wrists were affected. When admitted on August 17 there was only slight cardiac enlargement with an apical systolic murmur. Later a diastolic murmur developed. He was in hospital until November 7.

When first seen, in December 1938, there was a nodule on the right elbow. The apex beat was in the fourth intercostal space in the mid-clavicular line and there was a loud apical systolic murmur with a diastolic murmur at the aortic area and down the left sternal border. He was given a further period of rest and six weeks later the nodule had disappeared. The signs in the heart were unchanged except that the apical systolic murmur was softer. Since then he has remained well and there has been no change in the cardiac signs.

Fred was first examined in July 1939. He had no illness at the time his brother had acute rheumatism. On examination his heart was normal. Radiology shows that both have a similarly shaped heart, but that Harry's left ventricle is slightly larger. Their electrocardiograms are closely alike.

The evidence on which a diagnosis of monozygotic twins is based is as follows:

Facial appearance alike. Hair and eye colour identical. Both have a congenital sinus on the pinna of the right ear (a familial feature).

	Fred	Harry
Height	125·5 cm.	124·5 cm.
Weight	4 st.	4 st.
Head length	170 mm.	175 mm.
Head breadth	152 mm.	149 mm.
Blood group	A_2MN (negative to Pig. V_7D)	A_2MN (negative to Pig. V_7D)

Finger-prints. Right hand: first, fourth and fifth fingers similar. Left hand: first, second, third and fifth fingers similar. Dr. Stocks stated that some of the finger-prints were not clear enough to be sure of, but that the number of resemblances was six or seven. He had no doubt that the pair is monozygotic.

This pair shows the development of acute rheumatism and carditis with permanent damage to the aortic valve in only one of the twins. Thus, despite the same genetic constitution and the fact that the twins had been brought up and had lived nearly all their lives together, some undetermined factor caused an attack of rheumatism in one while the other escaped. Since diet, clothing, and housing were, as far as can be determined, identical in the two boys, chance exposure to infection appears to be the most probable way in which this could occur.

Summary and conclusions

Two pairs of apparently identical twins are described. In the first both children suffered a similar rheumatic attack following a sore throat, which in one only produced scarlet fever. In the second, one child only developed acute rheumatism and carditis although they had been brought up together. It is concluded that while heredity is of considerable importance in the causation of acute rheumatism, another factor, probably infection, plays an equally if not more important rôle.

Thanks are due to Mr. F. W. Willway and Mr. A. A. Dowling, the Surgical Registrars of the Bristol Royal Infirmary and Bristol Children's Hospital, for the information as to the appendicectomies in the second pair. I am also greatly indebted to Dr. G. L. Taylor of the Galton Laboratory, who kindly grouped the bloods, to Dr. Percy Stocks for advice on the finger-prints, and to Dr. Fraser Roberts, without whose help and advice the investigation of the twins would have been far less complete.

References

Kaufmann, O., and Scheerer, E. (1938). *Z. menschl. Vererb.-u.-Konst. Lehre*, **21**, 687.
Morgan, J. E., and Webster, S. J. (1938). *J. Amer. med. Ass.*, **110**, 1744.
Paul, J. R. (1931). *J. clin. Invest.*, **10**, 53.
Read, F. E. M., Ciocco, A., and Taussig, H. B. (1938). *Amer. J. Hyg.*, **27**, 719.
Roberts, J. A. F., and Thomson, W. A. R. (1934). *Ann. Eugen., Camb.*, **6**, 3.
Stocks, P. (1930). *Ibid.*, **4**, 49.
—— and Kara, M. (1933). *Ibid.*, **5**, 1.
Wilson, M. G., and Schweitzer, M. D. (1937). *J. clin. Invest.*, **16**, 555.

THE INCIDENCE OF THE FOUR MAIN BLOOD GROUPS IN RHEUMATIC HEART DISEASE

BY

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The familial incidence of acute rheumatism has long been recognized, but there is as yet no definite evidence as to whether this is due to similar environmental conditions, communicability of infection or to inherited predisposition. Wilson and Schweitzer (1937) concluded from their study that it was the last factor which was most important. Similar conclusions were reached by Roberts and Thomson (1934). Read, Ciocco and Taussig (1938) have also studied this problem and find that not only is rheumatic disease frequent among parents and siblings of rheumatic children, when there is both common inheritance and common environment, but that a similar frequency is observed in more distant relatives such as uncles, aunts and grand-parents who do not belong to the same immediate environment. However, the relatives probably belong to a similar walk of life as the patients and would thus be exposed to a similar if not the same environment. In view of this uncertainty it is obviously desirable to search for some somatic characteristic which might be associated with susceptibility to rheumatic infection. As long ago as 1903, Shrubsall suggested that the blonde types exhibited a special predilection for acute rheumatism, but Young (1933) in a careful study of rheumatic children was unable to confirm this. In addition, Young's study of the physical measurements, physical characters and relative bodily proportions revealed no significant differences between rheumatic and normal children.

Although these studies had provided negative results there are obviously other characteristics which might be associated with a predisposition to acute rheumatism. It therefore appeared desirable to determine the incidence of the main blood groups in patients with this disease. A similar study in some other diseases has already been made with doubtful results. Thus Grooten and Kossovitch (1929), Jungeblut and Smith (1932), Shaw, Thelander and Kilgareff (1933) and Hatzky (1933) have all investigated patients with, or convalescent from, acute anterior poliomyelitis with rather varying results. In patients with scarlet fever similar conflicting reports have been made by Minorescu and Stefanov (1926), Nowak (1932), Körwer (1932), Kiss and Teveli (1930) and Brody, Smith and Wolff (1936).

Method

In order to avoid any possible diagnostic errors only those patients were examined who showed undoubted evidence of rheumatic heart disease. Blood was collected in two tubes, one containing isotonic (3·7 per cent.) sodium citrate solution, the blood in the second tube being allowed to clot. Corpuscles from the citrated blood were grouped against standard A and B sera by the Vincet open slide method, the reaction being examined microscopically where necessary. The serum from the clotted blood was also grouped by the same method against known A and B corpuscles.

Results

Two hundred rheumatic patients were examined in this way and their blood groups found to be as follows: Group O: 94; group A: 89; group B: 12; and group AB: 5. Two series are available for comparison. The first is composed of 6,780 observations kindly provided by Drs. R. Race and G. L. Taylor of the Galton Laboratory and the other 4,388 observations kindly provided by Col. L. E. H. Whitby of the Army Blood Transfusion Service. The latter have the advantage of being drawn from the same district (Bristol and the West of England) as the patients with rheumatic heart disease. Both of these have been compared by the X^2 method, with the following results. Taking the figures supplied by Race and Taylor first:

	O	A	B	AB	TOTAL
Rheumatic heart disease sample	94	89	12	5	200
Race-Taylor's series	2941	2976	620	243	6780
Combined series	3035	3065	632	248	6980

Treating both series alike the expected figures are:

86·96	87·82	18·11	7·11
2948·04	2977·18	613·89	240·89

and the value of X^2:

0·570	0·016	2·061	0·626
0·017	0	0·061	0·018

$= 3·369$

Since there are three degrees of freedom Fisher's (1936) table shows that the probability lies between 0·30 and 0·50 and the difference between the two is of no singificance.

Treating the controls provided by Whitby in the same manner:

	O	A	B	AB	TOTAL
Rheumatic heart disease sample	94	89	12	5	200
Whitby's series	2137	1818	304	129	4388
Combined series	2231	1907	316	134	4588

For these the expected figures are:

97·25	83·13	13·78	5·84
2133·75	1823·87	302·22	128·16

and the value of X^2:

0·109	0·414	0·230	0·121
0·005	0·019	0·010	0·006

$=0·914$

which with three degrees of freedom indicates a probability between 0·80 and 0·90.

There is thus no evidence that a genetic predisposition to rheumatic heart disease is associated with any of the four main blood groups.

Summary

The blood groups of two hundred patients with rheumatic heart disease have been determined. The distribution of these blood groups does not differ from that in the general population.

Thanks are due to Dr. Fraser Roberts for advice about the statistical analysis of the figures.

REFERENCES

Brody, H., Smith, L. W., and Wolff, W. I. (1936). *J. Lab. clin. Med.*, **21,** 705.
Fisher, R. A. (1936). *Statistical Methods for Research Workers, Sixth Edition*, Edinburgh.
Grooten, O., and Kossovitch, N. (1929). *C. R. Soc. Biol., Paris*, **105,** 428.
Hatzky, K. (1933). *Münch. med. Wschr.*, **80,** 1973.
Jungeblut, C. W., and Smith, L. W. (1932). *J. Immunol.*, **23,** 35.
Kiss, P., and Teveli, Z. (1930). *Jhb. Kinderheilk.*, **127,** 110.
Körwer, H. (1932). *Ibid.*, **136,** 59.
Minorescu, T., and Stefanov, G. (1926). *C. R. Soc. Biol., Paris*, **95,** 140.
Nowak, H. (1932). *Msch. Kinderheilk.*, **54,** 343.
Read, F. E. M., Ciocco, A., and Taussig, H. B. (1938). *Amer. J. Hyg.*, **27,** 719.
Roberts, J. A. F., and Thomson, W. A. R. (1934). *Ann. Eugen. Camb.*, **6,** 3.
Shaw, E. B., Thelander, H. E., and Kilgareff, K. (1933). *Amer. J. Dis. Child.*, **49,** 99.
Shrubsall, F. C. (1903). *St. Bart's Hosp. med. Rep.*, **39,** 63.
Wilson, M. G., and Schweitzer, M. D. (1937). *J. clin. Invest.*, **16,** 555.
Young, M. (1933). *J. Hyg., Camb.*, **33,** 435.

CARBOHYDRATE TOLERANCE IN HYPO-THYROIDISM AND HYPERTHYROIDISM

BY

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Since the beginning of the present century it has been recognized that disturbances of thyroid secretion are associated with characteristic alterations of the carbohydrate tolerance (Knöpfelmacher, 1904; von Noorden, 1910), and current views upon the nature of the changes remain substantially unaltered.

Thus Leyton (1937), in Price's textbook, writes that in hypothyroidism there is considerable increase in the tolerance for dextrose, whilst Beaumont (1937) states that in hypothyroidism sugar tolerance is increased, but that in hyperthyroidism sugar tolerance is often diminished. Similar statements may be found in almost any general textbook of medicine.

Reports of experimental work, however, reveal less unanimity of opinion. Janney and Isaacson (1918) and von Noorden and Isaac (1927) observed that in hypothyroidism the blood-sugar curve after oral glucose was of flatter type than in normal subjects, and the former workers showed also that the curve became normal under thyroid gland therapy. Knöpfelmacher (1904) had previously demonstrated an increased assimilation limit for glucose in cases of myxoedema. Gardiner-Hill, Brett and Smith (1925), on the other hand, obtained precisely opposite results: in fifteen myxoedematous adults they found the blood-sugar curve to be both higher and more prolonged than in normal subjects, whilst administration of thyroid gland substance lowered and shortened the curve. Diminished oral glucose tolerance in hypothyroidism was found also by Flesch (1913) and Gray (1923).

Concerning hyperthyroidism there is more general agreement. Denis, Aub and Minot (1917), Janney and Isaacson (1918), Gardiner-Hill, Brett and Smith (1925), von Noorden and Isaac (1927), Torday (1927) and Joslin (1928) all observed a protracted hyperglycaemia, frequently associated with glycosuria, after oral administration of glucose to the subjects of toxic goitre. Attempting to explain this loss of tolerance to oral glucose Cramer and Krause (1912) and Coggeshall and Greene (1933) have demonstrated that animals receiving excess thyroid gland fail to store glycogen in the liver and muscles. Griffiths (1939), using a combined insulin-glucose test, claims to have demonstrated that in toxic and non-toxic goitre there is marked peripheral resistance to insulin action and a slighter degree of central resistance.

Investigations of these problems in children have been scanty; Svensgaard (1931) studied the oral glucose tolerance of four untreated cretins, and in two of the cases she repeated the test after thyroid treatment had been established.

The blood-sugar curves after oral glucose (2 grammes per kgm. of body weight) were low in the untreated cretins, the maximum elevation above the fasting level varying from 43 to 82 mgm. per 100 c.c. In the two patients in whom the test was repeated after thyroid treatment was well established, rises of 133 and 170 mgm. per 100 c.c. were obtained, with maximum hyperglycaemic levels of 204 and 254 mgm. per 100 c.c. Perusal of the literature has not disclosed any reports of investigations of carbohydrate metabolism in children with hyperthyroidism.

The present investigation has been conducted in an attempt to determine the nature of the changes of carbohydrate tolerance brought about by conditions of hypo- and hyperthyroidism in children, and to explain, as far as possible, the manner in which these changes are produced. Children are particularly suitable subjects for this study, for in them the lesions usually occur in a pure form, so that the metabolic disturbances noted can be assumed to depend upon the altered state of the thyroid secretion. In adult myxoedematous subjects, on the other hand, conflicting factors, such as arteriosclerosis and post-menopausal polyglandular disturbances, are frequently present and tend to distort the results of metabolic tests and to render their interpretation more difficult.

Methods of investigation

As gauges of glucose tolerance, two tests have been employed:

1. The oral glucose tolerance test. For this procedure a test dose of 2·0 grammes glucose per kgm. body weight was employed for children under three years of age, and a dose of 1·0 gramme glucose per kgm. body weight for older children. The sugar was given as a 10 per cent. solution in water, the child having fasted from the previous night—a period of twelve to fifteen hours. The capillary blood sugar content was estimated on samples taken fasting and at fifteen-minute intervals for two hours after the glucose administration, and the urine was examined for sugar one and two hours after the test dose, or, in the younger subjects, whenever a specimen could be obtained. In estimating the results of these tests (tables 2 and 4) the following arbitrary standards have been used for descriptive purposes:

A. Low curve: maximum increase in blood-sugar concentration of 30 mgm. per 100 c.c. or less.
B. Low-normal curve: maximum rise of 30 to 50 mgm. per 100 c.c.
C. Normal curve: maximum rise of 50 to 85 mgm. per 100 c.c.
D. High-normal curve: maximum rise of 85 to 100 mgm. per 100 c.c.
E. High curve: a rise of more than 100 mgm. per 100 c.c.

2. The intravenous glucose tolerance test. The value of the intravenous test and its advantages over the oral test have been frequently emphasized (Crawford, 1938, 1939; Ross, 1938; Tunbridge and Allibone, 1940), and it is now coming into general use as a method of investigation of carbohydrate tolerance. Owing to the wide variations between the results of previous workers, variations probably due to differences in technique, the present investigations were preceded by a detailed examination of the response of healthy children and adults to the intravenous injections of glucose. This work has already been published (Crawford, 1938) and the following is a brief description of the standard test used in this and in the previous investigations, and of the findings in normal subjects.

A test dose of 0·5 gramme of glucose per kgm. body weight, dissolved in

normal saline to form a 20 per cent. solution, is injected intravenously following an eight-hour fast. Capillary blood is removed for sugar estimation prior to the injection, two minutes after its completion and at fifteen-minute intervals until ninety minutes after the injection. Tolerance is gauged by noting the time after the injection at which the blood sugar concentration returns to a value of 100 mgm. per 100 c.c. or less—the upper limit of normal fasting blood-sugar values with the technique employed. The time at which this occurs was shown to be constant for the individual under standard conditions and to vary within definite limits among normal subjects. It was shown that in health the blood-sugar reached a level of 100 mgm. per 100 c.c. at thirty, forty-five, sixty, or seventy-five minutes after the injection according to the age of the subject (table 1). The amount of sugar excreted in the urine varied from 3 to 9 per cent of the injected glucose.

TABLE 1

INTRAVENOUS GLUCOSE TOLERANCE TESTS IN NORMAL SUBJECTS

AGE GROUP	TIME OF FALL OF BLOOD-SUGAR TO 100 MGM. PER 100 C.C.
0–2 years	30–45 minutes
2–4 years	45–60 minutes
4–10 years	45–75 minutes
Over 10 years	60–75 minutes

Blood-sugar estimations were made by a modification of the method of Hagedorn and Jensen (1923), urinary estimations by the method of Benedict (1911).

Cretinism

Six cases of cretinism (congenital hypothyroidism or athyroidism) have been investigated as regards their tolerance to oral glucose before and after the start of treatment with thyroid gland preparations. In five of these cases, and in two older cretins who had been under treatment for several years, intravenous tolerance tests were also carried out. Subjects are designated as ' untreated ' prior to the start of thyroid gland administration and as ' treated ' when they had been receiving adequate amounts of thyroid gland for two weeks or longer and showed definite evidence of clinical improvement.

THE FASTING BLOOD-SUGAR LEVEL was estimated on fifteen occasions on untreated subjects and on nineteen occasions after treatment was established. The values prior to treatment ranged from 45 to 88 mgm. per 100 c.c., with a mean value of 60·8 mgm. Four were below 50, and a further four below 60 mgm. per 100 c.c. In treated subjects the fasting blood-sugar levels ranged from 50 to 99 mgm. per 100 c.c. with a mean value of 71·0 mgm. In none of the treated cases was a level below 50 recorded, but in six of them the fasting value was below 60 mgm. per 100 c.c. Thus, while a marked tendency to low fasting blood-sugar levels was found in untreated cretins, with more normal values occurring after treatment, great irregularity was observed—some normal values occurred in untreated and some subnormal values in treated cases.

THE ORAL GLUCOSE TOLERANCE TESTS. The results of these tests are recorded in table 2. The irregularity of the response of young children to the oral administration of glucose, and the consequent difficulties in the interpreta-

tion of the results of oral glucose tolerance tests, have been frequently emphasized (Svensgaard, 1931; Crawford, 1938; Ross, 1938), and they are well exemplified in the present series of tests. Three of the cases (1, 2 and 4) showed, before treatment, a well-marked low curve, while a fourth (case 5) gave a low-normal curve. Case 3 showed a high curve, and case 6 a high curve twice and a normal curve once. It is thus clear that the response to oral glucose in cretinous children is variable; whilst the blood-sugar curve tends most frequently to be depressed, normal and high curves may occur and there may be great variation from time to time in the same subject.

The effect of thyroid gland therapy on oral glucose tolerance also varied greatly from case to case. In case 1 the low curve present before treatment was elevated to a low-normal curve after two weeks of treatment, and the low curve was restored when treatment was withheld at a later date. The low curve in case 2 rose to a low-normal curve after three weeks of treatment and to a normal curve after seven weeks. In case 4 the low curve remained low after four weeks of treatment, though the blood-sugar rise had increased from 14 to 26 mgm. per 100 c.c. The low-normal curve present before treatment in case 5 changed, after four weeks of treatment, to a high curve and glycosuria occurred. Some tachycardia was present at the time of the second test, and it is possible that the dosage of thyroid gland was then excessive. In case 3 the high curve of the period before treatment was changed to a low-normal curve after two weeks of treatment and to a normal curve after four weeks; whilst in case 6 the findings were as irregular on treatment as they had been before treatment was commenced; two high curves and a normal curve were obtained, though there were no signs of thyroid over-dosage. Case 7, an older cretin treated regularly for nine years, gave a normal curve.

From these results it would seem that the general effect of thyroid treatment on the abnormal oral glucose tolerance curves of cretinism is to cause a movement in the direction of normality. Low curves before treatment were constantly raised by treatment; but in cases not showing the low curve the effect was irregular. The curves from case 2, representing what may be regarded as the typical findings in cretinism, are charted in fig. 1.

Intravenous Glucose Tolerance Tests were performed in five of the cases before and after starting treatment and also in two older cretins who had received continuous thyroid treatment for three and nine years respectively. The results of these tests are detailed in table 3. Prior to the start of treatment every case showed a delay in the fall of the blood-sugar level to normal fasting values. The extent of the delay varied from case to case. Cases 4 and 5 showed only slight delay, the fall occurring in sixty minutes in the former (normal for age, thirty to forty-five minutes) and in seventy-five minutes in the latter (normal, forty-five to sixty minutes). In cases 2 and 6 the delay was of greater degree (fall in seventy-five minutes, normal in thirty to forty-five minutes), whilst in case 3 there was gross impairment of tolerance to intravenous glucose, a normal fasting level not having been reached in the ninety-minute specimen.

Treatment with thyroid gland preparations caused a change to a normal

TABLE 2

RESULTS OF ORAL GLUCOSE TOLERANCE TESTS IN CASES OF CRETINISM

CASE	AGE		BLOOD-SUGAR : MGM. PER 100 C.C.						CLINICAL CONDITION	TYPE OF CURVE
	YEARS	MONTHS	FASTING	½ HR.	1 HR.	1½ HRS.	2 HRS.	MAXIMUM RISE		
1	1	6	45	52	52	45	43	7	Untreated	Low
			51	56	64	57	52	13	Untreated	Low
			81	125	86	75	57	44	Treated 2 weeks.	Low-normal
			63	65	77	61	53	14	Treatment stopped 1 week	Low
			59	53	56	49	63	4	Treatment stopped 3 weeks	Low
2		4	48	56	69	71	63	23	Untreated	Low
			56	69	96	80	69	40	Treated 3 weeks	Low-normal
			50	125	135	121	91	85	Treated 7 weeks	Normal
3	2	7	56	104	166	188	143	132	Untreated	High
			65	90	110	99	101	45	Treated 2 weeks	Low-normal
			75	92	113	134	99	59	Treated 4 weeks	Normal
4	1		67	64	81	65	67	14	Untreated	Low
			60	86	78	77	62	26	Treated 3 weeks	Low
5	4	7	72	99	102	101	106	34	Untreated	Low-normal
			79	97	138	204	184	125	Treated 4 weeks, ? dose excessive	High*
6	1	0	66	175	204	200	209	143	Untreated	High*
	1	6	75	129	122	74	65	54	Untreated	Normal
			63	152	206	179	164	143	Untreated	High*
			99	226	190	122	86	127	Treated 3 weeks	High*
			90	158	163	119	101	73	Treated 3 months	Normal
			70	181	110	83	81	111	Treated 4 months	High
7	9	6	50	83	111	72	60	61	Treated 9 years	Normal

* Glycosuria.

TABLE 3

RESULTS OF INTRAVENOUS GLUCOSE TOLERANCE TESTS IN CASES OF CRETINISM

CASE	AGE		BLOOD-SUGAR : MGM. PER 100 C.C.								CLINICAL CONDITION	TYPE OF CURVE
	YEARS	MONTHS	FASTING	2 MINS.	15 MINS.	30 MINS.	45 MINS.	60 MINS.	75 MINS.	90 MINS.		
2		4	55	372	266	188	140	101	84	66	Untreated	Markedly delayed fall
			53	347	206	140	98	87	59	61	Treated 4 weeks	Normal curve
3	2	7	57	262	200	168	155	141	136	124	Untreated	Grossly delayed fall
			102	336	217	161	131	111	83	83	Treated 4 weeks ; dose excessive	Delayed fall
			72	251	186	83	50	43	52	61	Treated 8 weeks ; dose adjusted	Rapid-normal fall
4	1		48	376	278	170	102	55	—	—	Untreated	Delayed fall
			55	401	313	197	133	66	—	—	Treated 3 weeks	Delayed fall
5	4	7	76	300	199	145	122	104	79	75	Untreated	Delayed fall
			81	343	243	193	164	119	97	83	Treated 4 weeks ; ? dose excessive	Delayed fall
6	1		88	310	188	141	124	104	86	84	Untreated	Markedly delayed fall
			93	257	148	104	90	81	68	—	Treated 3 weeks	Normal curve
			90	284	163	124	104	85	74	77	Treated 4 weeks ; dose excessive	Delayed fall
7	9	6	46	357	210	135	88	62	51	44	Treated 9 years	Normal curve
8	6	10	68	333	217	154	103	70	60	—	Treated 3 years	Normal curve

intravenous glucose tolerance curve in three of the five cases (cases 2, 3 and 6), and normal curves were also found in the two older treated cretins (cases 7 and 8). In cases 4 and 5 no improvement of intravenous tolerance occurred, the descent of the blood-sugar curve remaining slow after the start of treatment, though in case 5 this may have been due to excessive dosage of thyroid, as pointed out above in connexion with the oral curves in this case. In two cases (cases 3 and 6) intravenous glucose tolerance curves were obtained at a time when definite clinical evidence of overdosage with thyroid gland was present.

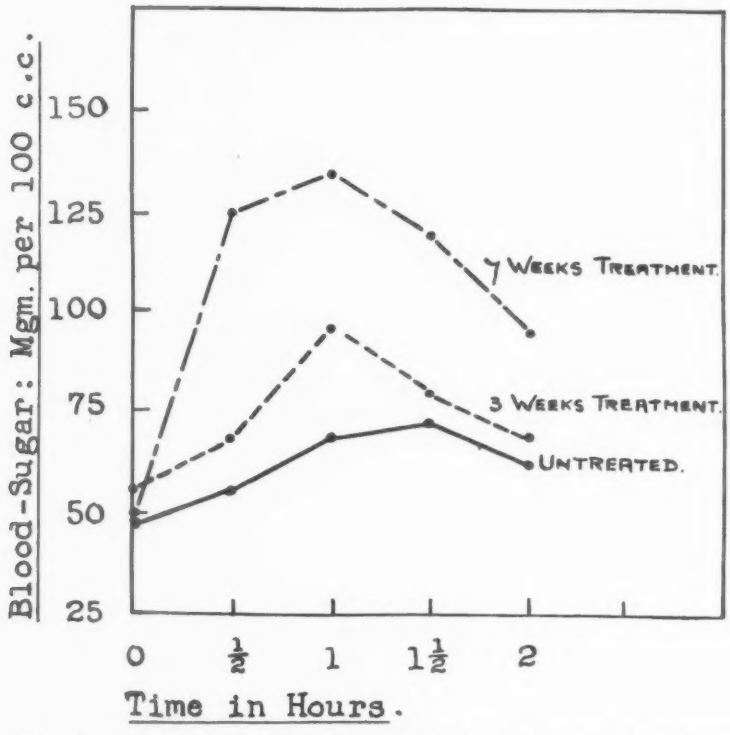

FIG. 1.—Case 2. Cretin: Oral glucose tolerance curves before and after commencing treatment.

In each instance the fall of the blood-sugar curve was delayed, but a normal curve was obtained by appropriate adjustment of the thyroid dosage.

From these results it appears that in cretinism the tolerance for intravenous glucose is diminished, but that normal tolerance can be restored by treatment with the correct dosage of thyroid gland. If too much thyroid is given impairment of tolerance reappears. As examples of these typical findings the curves from case 6 are shown in fig. 2.

Hyperthyroidism

Hyperthyroidism is not a common condition in childhood, but the opportunity has arisen of investigating two cases. In the first (case 9), a boy aged six-and-a-half years, enlargement of the thyroid gland was occasioning some discomfort and on investigation signs of mild hyperthyroidism were found.

Unfortunately the child died of diphtheria a few months after he was first seen. The second case (case 10) was one of severe exophthalmic goitre in a girl aged ten years and four months. No abatement of the condition occurred during the period of observation. It has thus been possible to observe the tolerance to oral and intravenous glucose in two cases of active hyperthyroidism, one mild and one severe. The results of the tests are recorded in tables 4 and 5, and in fig. 3 the curves from the severe case are shown. After oral administration of glucose case 9 yielded a normal blood-sugar curve, but in case 10 the curve was high and glycosuria occurred. After intravenous glucose the return of the

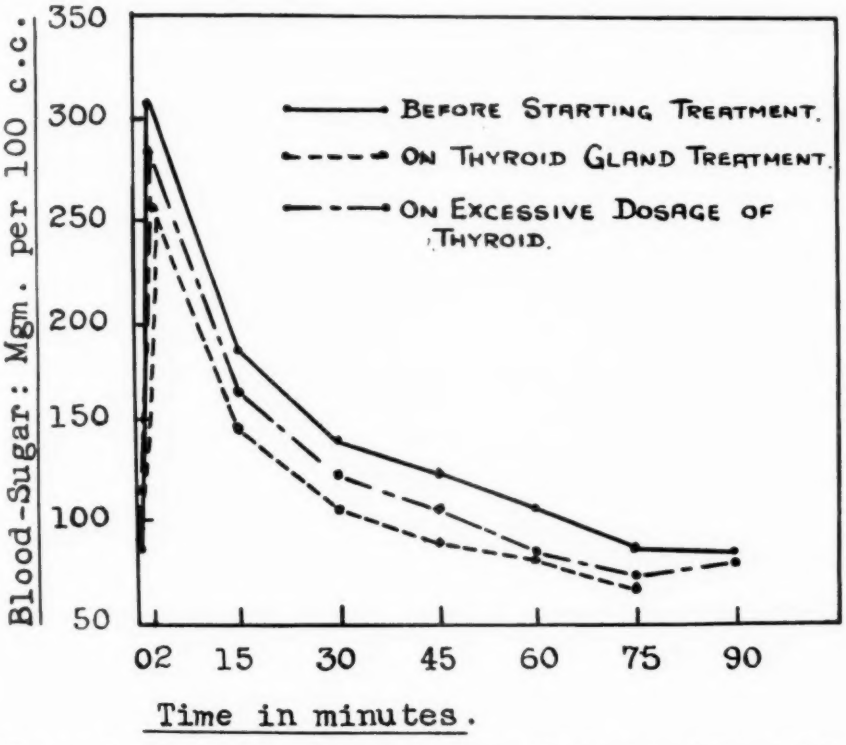

FIG. 2.—Case 6. Cretinism: Intravenous glucose tolerance curves before and after commencing treatment.

blood-sugar concentration to within normal limits was delayed in each case, indicating impairment of tolerance.

Summary of results

In cretinism the following features of the carbohydrate metabolism have been observed:

1. The fasting blood-sugar level is frequently subnormal, tending to rise under treatment with thyroid preparations.

2. Results of oral glucose tests are irregular. Low curves are of frequent occurrence, but normal and high curves also occur.

3. Intravenous glucose tolerance tests show, constantly, impairment of

TABLE 4

RESULTS OF ORAL GLUCOSE TOLERANCE TESTS IN HYPERTHYROIDISM

CASE	AGE		BLOOD-SUGAR : MGM. PER 100 C.C.						CLINICAL CONDITION	TYPE OF CURVE
	YEARS	MONTHS	FASTING	½ HR.	1 HR.	1½ HRS.	2 HRS.	MAXIMUM RISE		
9	6	6	81	105	140	106	83	59	Mild hyperthyroidism	Normal
10	10	4	83	222	174	167	77	139	Severe hyperthyroidism	High : glycosuria

TABLE 5

RESULTS OF INTRAVENOUS GLUCOSE TOLERANCE TESTS IN HYPERTHYROIDISM

CASE	AGE		BLOOD-SUGAR : MGM. PER 100 C.C.								CLINICAL CONDITION	TYPE OR CURVE
	YEARS	MONTHS	FASTING	2 MINS.	15 MINS.	30 MINS.	45 MINS.	60 MINS.	75 MINS.	90 MINS.		
9	6	6	97	336	219	193	154	129	108	99	Mild hyperthyroidism	Delayed fall
10	10	4	88	316	226	163	132	120	108	92	Severe hyperthyroidism	Delayed fall

glucose tolerance; this contrasts strongly with the usual assertion that tolerance to carbohydrate is increased in hypothyroidism.

4. Under treatment all the curves tend to approach normal; but if excessive dosage of thyroid gland is given impairment of tolerance reappears in the form of high oral and delayed intravenous curves.

5. Two cases of hyperthyroidism were studied. One case showed a high oral

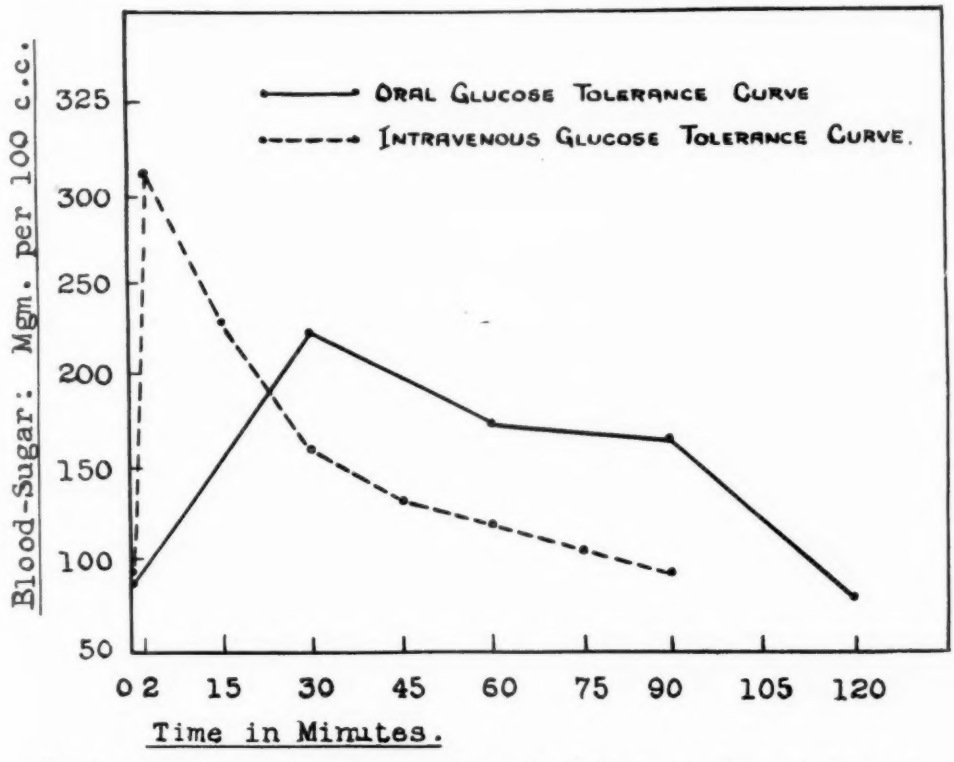

FIG. 3.—Case 10. Blood-sugar curves after oral and intravenous glucose in a case of exophthalmic goitre.

curve, with glycosuria; in the other the oral curve was within normal limits. Both exhibited impaired tolerance to intravenous gucose.

Discussion

The results recorded above present three rather paradoxical findings: first, the occurrence of both high and low oral glucose tolerance curves in untreated cretins; second, the fact that in untreated cretins the constantly occurring impaired tolerance to intravenous glucose has frequently been found associated with a low oral curve—the so-called ' increased tolerance to glucose ' of the textbooks; and third, the observation that such diametrically opposed conditions as cretinism on the one hand, and hyperthyroidism on the other, both are associated with impairment of intravenous glucose tolerance.

Consideration of the factors which determine the nature of the curves obtained after oral and intravenous administration of glucose offers an explana-

tion of these apparently contradictory findings. Following oral glucose, the height and form of the blood-sugar curve depend upon:

1. The rate of absorption of the glucose from the alimentary canal.
2. The rate at which glucose oxidation is proceeding.
3. The rate at which the absorbed glucose is laid down as glycogen in the liver and muscles.

With intravenous administration of the glucose the absorption factor is eliminated and the duration of the hyperglycaemia depends upon the rates of oxidation and storage only.

Confusion in the interpretation of the results of intravenous glucose tolerance tests may arise from the fact that different abnormalities of the intermediary carbohydrate metabolism can produce the same alteration of the blood-sugar curve obtained. Thus increased formation of glycogen and increased oxidation of glucose both lead to a rapidly falling curve; whilst increased breakdown of glycogen, diminished formation of glycogen and diminished oxidation of glucose all result in abnormally prolonged curves.

The irregular response of cretins to the oral administration of glucose and the constantly high intravenous glucose tolerance curves suggest that it is the latter which reflects the true state of the carbohydrate tolerance of these children. Impairment of tolerance seems the more logical result of the slowing of the metabolic processes in general, which is known to occur in conditions of thyroid deficiency, than does the increased tolerance which some of the oral curves suggest. If this is correct then it is probable that the low oral glucose curves result from slow or faulty absorption of glucose from the bowel, being analogous to the low oral curves of idiopathic steatorrhoea (Thaysen, 1932; Crawford, 1939). That some such faulty or delayed absorption exists seems not unlikely, for constipation and abdominal distension are almost constant features of cretinism. It was frequently observed that the stomach was as full and prominent at the end of the oral tolerance test as it had been immediately after administration of the dose of glucose. Sluggishness of the movements of the alimentary canal, myxoedema of the bowel wall, and torpidity of the portal circulation may all play some part in the delayed absorption.

The occasional occurrence of high oral curves in hypothyroidism, as recorded by Flesch (1913), Gray (1923) and Gardiner-Hill, Brett and Smith (1925), and as observed in cases 3 and 6 of the present series, is explicable by the assumption that in these cases unusually rapid absorption of glucose from the bowel has occurred and has thus unmasked the impaired carbohydrate tolerance which the intravenous test has shown to be present. That the rate of intestinal absorption is in children both variable and uncontrollable has already been pointed out (Crawford, 1938). In addition, it may be that variations in the amount of myxoedematous tissue from case to case lead to considerable differences in the proportion of glucose dosage to metabolically active tissue, when body weight is used as the basis for dosage.

As regards the occurrence of impaired tolerance to glucose as demonstrated by the intravenous test in conditions of both hypo- and hyperthyroidism, an explanation is readily available. In hypothyroidism the delayed fall of the

curve reflects the effect on carbohydrate metabolism of the general slowing of the metabolic processes of the body: there is certainly a diminution in the rate of glucose oxidation, and it is probable that the rate at which the injected glucose is stored as glycogen is also slowed. Carbohydrate metabolism in conditions of hyperthyroidism, both clinical and experimental, has been extensively investigated.

Many workers (Cramer and Krause, 1912; Cramer, 1916; Cramer and McCall, 1916; Kuriyama, 1917; Coggeshall and Greene, 1933) have shown that hyperthyroidism produced in animals by thyroid feeding leads to a rapid discharge of the liver glycogen. Cramer and Krause (1912) found glycogen absent from the liver of thyroid-fed animals, even when they were maintained on a high carbohydrate diet and the liver was examined shortly after a meal. Muscle glycogen was also found to be diminished in amount. Seeking the cause of this inhibition of glycogen storage in thyroid-fed animals, and basing their work on the original demonstration by Eppinger, Falta and Rudinger (1908) of the close relationship existing between thyroid and suprarenal activity, Hoskins (1910), Herring (1916, 1917) and Cramer (1918) have found evidence of hypertrophy and increased activity of the suprarenal medulla. Broking and Trendelenburg (1911) actually demonstrated an increase of the adrenaline content of the blood of patients suffering from exophthalmic goitre, and Cannon, Binger and Fitz (1915) succeeded in producing the syndrome of hyperthyroidism in cats by the operation of unilateral phrenico-sympathetic anastomosis. From his own observations as well as those of other workers Cramer (1918) concluded that hyperthyroidism is in effect a slight but definite hyperadrenalism, though Asher and Flack (1910, a and b) and Levy (1916) recorded observations from which they concluded that excessive thyroid secretion rendered the tissues hypersensitive to the action of adrenaline, even in normal amounts. More recently Himsworth (1939) has put forward the hypothesis that the anterior-pituitary hormones are concerned in the production of the defective hepatic glycogen storage which occurs in hyperthyroidism. In his view the raised metabolic rate causes an increased demand by the tissues for sugar; this stimulates the anterior-pituitary gland to secrete in excess the factor concerned in carbohydrate metabolism, and this in turn leads to increased breakdown of hepatic glycogen.

Whichever of these views is regarded as correct, it is clear that the impaired carbohydrate tolerance, both oral and intravenous, in conditions of hyperthyroidism results from interference with the normal storage of the ingested or injected glucose as glycogen. Though the rate of oxidation of glucose may be actually increased (Cramer and McCall, 1917), the effect of this on the total tolerance is overshadowed by the failure of glycogen storage.

As was to be expected, the predominant effect of thyroid gland therapy on the abnormal tolerance curves of hypothyroidism was a move towards normal values; but if too great a dose of thyroid substance were employed (cases 3 and 6) impairment of tolerance recurred. The case was in fact converted by this excessive dosage to one of hyperthyroidism. These findings suggest the possibility of employing the intravenous glucose tolerance test as a gauge for the correct dosage of thyroid substance for any given case. The optimum dose would be the greatest amount compatible with a normal intravenous curve.

Conclusions

In conditions of hypothyroidism carbohydrate tolerance is impaired. This impairment is due to a general slowing of the processes of katabolism, and possibly also to a diminution in the rate of storage of carbohydrate. The low oral blood-sugar curve which occurs frequently, and which accounts for the text-book statements that carbohydrate tolerance is increased in hypothyroidism, is due to slow absorption of the carbohydrate from the bowel.

In hyperthyroidism also there is impairment of carbohydrate tolerance, the fault being traceable to defective glycogen formation. This probably results from the excessive secretion of thyroxin causing an increased liberation of adrenaline, which in its turn mobilizes hepatic glycogen and inhibits its reformation.

Thanks are due to Professor G. B. Fleming for his valuable criticism and advice, and to the clinical and biochemical staffs at the Hospital for the assistance which they have given.

The expenses incurred in this investigation were defrayed by a grant from the Medical Research Council.

Case summaries

Case 1. M. McM. Female, aged one year six months. Complaint: failure to grow since the age of six months. History: appeared normal at birth; throve until the age of six months, since when growth has been defective; sleeps excessively; is not walking or talking; has not cut any teeth; constipated. Examination: weight 8·5 kgm. (normal for age 10·0 kgm.); height 68 cm. (normal 77 cm.); appears dull mentally; skin dry and coarse, with thickened subcutaneous tissues; tongue large and frequently protruded; small umbilical hernia. Blood: red blood cells, 3,750,000 per c.mm.; haemoglobin 68 per cent. Carpal ossification: no centres (normal for age, three centres).

Case 2. M. C. Female, aged four months. Complaint: difficulty in feeding; mental backwardness. History: infant appeared healthy until the age of three months, when progress ceased and she became listless, constipated and disinclined for her feeds. Examination: weight 4·8 kgm. (normal 5·6 kgm.); skin dry; features coarse and cretinoid; hoarse cry; some nasal obstruction; supraclavicular pads of fat. Blood: red blood cells 2,400,000 per c.mm.; haemoglobin 50 per cent. Carpal ossification: no centres.

Case 3. A. McM. Female, aged two years seven months. Complaint: failure to walk and talk. History: throve normally until the age of nine months; subsequent development slow; sleeps excessively and makes no attempt to talk or walk; constipated. Examination: weight 9 kgm. (normal 13 kgm.); height 70 cm. (normal 86 cm.); protruding tongue; skin dry and myxoedematous; hoarse cry. Blood: red blood cells 2,950,000 per c.mm.; haemoglobin 63 per cent. Carpal ossification: one centre (normal three to four centres).

Case 4. H. W. Female, aged one year. Complaint: slow development. History: appeared normal at birth, but progress was very slow; talking and walking have not commenced; constipated. Examination: weight 7·45 kgm. (normal 9·8 kgm.); skin dry; broad cretinoid facies, with large protruded tongue; umbilical hernia. Blood: red blood cells 3,170,000 per c.mm.; haemoglobin 60 per cent. Carpal ossification: no centres (normal two centres).

Case 5. M. W. Female, aged four years seven months. Complaint: failure to grow. History: following a normal birth child grew very slowly; first tooth at one year three months; walking began at two years; speech still

very defective. Examination: weight 13·7 kgm. (normal 16·8 kgm.); height 82 cm. (normal 93 cm.); skin dry and myxoedematous; facies typically cretinoid; primary dentition fully erupted, but carious. Blood: red blood cells 4,100,000 per c.mm.; haemoglobin 84 per cent. Carpal ossification: four centres (normal seven centres).

Case 6. S. M. Male, aged one year. Complaint: failure to thrive since the age of two months. History: birth normal; child seemed well up to age of two months, after which made little progress; cannot sit up and has cut no teeth. Examination: weight 5·8 kgm. (normal 9·3 kgm.); height 61 cm. (normal 74 cm.); dry skin; thick, protruding tongue, coarse features; hoarse low-pitched cry; supraclavicular pads of fat; umbilical hernia. Blood: red blood cells 4,460,000 per c.mm.; haemoglobin 68 per cent. Carpal ossification: no centres (normal two centres).

Case 7. A. G. Female, aged nine and a half years. Attended hospital for the supply of thyroid tablets, which she had received from various clinics since the age of six months, when cretinism was diagnosed at a maternity hospital infant clinic. On thyroid treatment made slow progress: first tooth appeared, and talking began, at age of one year; walked alone at age of two years. She is rather backward at school. Examination: weight 26 kgm. (normal 28 kgm.); height 120 cm. (normal 129) cm.; appears healthy—not obviously a cretin; intelligence quotient 58 per cent.; umbilical herniotomy scar present. Carpal ossification normal.

Case 8. S. C. Female, aged six years ten months. Diagnosed as a cretin in hospital at the age of four years—then not talking or walking, and appearance described as typically cretinoid. Since then on regular thyroid treatment, and has made good progress. Examination: weight 16·8 kgm. (normal 21 kgm.); height 102 cm. (normal 116 cm.); mental condition good (intelligence quotient 80 per cent.); no anaemia. Carpal ossification: six centres (normal eight to ten centres).

Case 9. P. M. Male, aged six and a half years. Complaint: swelling in the neck and difficulty in swallowing. History: recurrent attacks of swelling in the neck, sometimes with dysphagia, since the age of three years. Examination: weight 23·6 kgm. (normal 22 kgm.); height 124 cm. (normal 115 cm.); well-developed child; thyroid gland enlarged and firm, especially the isthmus; slight exophthalmos; definite fine tremor of hands; pulse rate not increased. Died of diphtheria nine months after the investigations were made.

Case 10. E. C. Female, aged ten years four months. Complaint: nervousness and excitability. History: for a year her eyes had gradually increased in prominence, and for a month nervousness had been extreme. Examination: weight 24·2 kgm. (normal 30 kgm.); height 131 cm. (normal 133 cm.); well developed but thin child; highly emotional and nervous; severe exophthalmos; sweating marked; moderate uniform enlargement of thyroid gland; pulse rate 110 to 140 per minute; tremor of hands; basal metabolic rate: +78 per cent.

References

Asher, L., and Flack, M. (1910a). *Zbl. Physiol.*, **24,** 211.

—— —— (1910b). *Z. Biol.*, **55,** 83.

Beaumont, G. E. (1937). *Medicine*, third edition, London.

Benedict, S. R. (1911). *J. Amer. med. Ass.*, **57,** 1193.

Broking, E., and Trendelenburg, P. (1911). *Dtsch. Arch. klin. Med.*, **103,** 168.

Cannon, W. B., Binger, C. A. L., and Fitz, R. (1915). *Amer. J. Physiol.*, **36,** 363.

Coggeshall, H. C., and Greene, J. A. (1933). *Ibid.*, **105,** 103.

Cramer, W. (1916). *J. Physiol.*, **50,** 38.

—— (1918). *Ibid.*, **52,** 8.

Cramer, W., and Krause, R. A. (1912). *Proc. roy. Soc., B.*, **86,** 550.
—— and McCall, R. (1916). *J. Physiol.*, **50,** 36.
——, —— (1917). *Quart. J. exp. Physiol.*, **11,** 59.
Crawford, T. (1938). *Arch. Dis. Childh.*, **13,** 69.
—— (1939). *Quart. J. Med.*, **8,** 251.
Denis, W., Aub, J. C., and Minot, A. S. (1917). *Arch. intern. Med.*, **20,** 964.
Eppinger, H., Falta, W., and Rudinger, C. (1908). *Z. klin. Med.*, **66,** 1.
Flesch, M. (1913). *Beitr. klin. Chir.*, **82,** 236.
Gardiner-Hill, H., Brett, P. C., and Smith, J. F. (1925). *Quart. J. Med.*, **18,** 327.
Gray, H. (1923). *Arch. intern. Med.*, **31,** 259.
Griffiths, W. J. (1939). *Quart. J. Med.*, N.S. **8,** 23.
Hagedorn, H. C., and Jensen, I. (1923). *Biochem. Z.*, **135,** 46.
Herring, P. T. (1916). *Quart. J. exp. Physiol.*, **9,** 391.
—— (1917). *Ibid.*, **11,** 47.
Himsworth, H. P. (1939). *Lancet*, **2,** 65.
Hoskins, R. G. (1910). *J. Amer. med. Ass.*, **55,** 1724.
Janney, W. W., and Isaacson, V. J. (1918). *Arch. intern. Med.*, **22,** 160.
Joslin, R. (1928). *The Treatment of Diabetes Mellitus*, London.
Kuriyama, S. (1917). *Amer. J. Physiol.*, **43,** 381.
Knöpfelmacher, W. (1904). *Wien. klin. Wschr.*, **17,** 244.
Levy, R. L. (1916). *Amer. J. Physiol.*, **41,** 492.
Leyton, O. (1937). *Textbook of the Practice of Medicine* (Edited by Price, F. W.) fifth edition. London.
Noorden, C. von. (1910). *Die Fettsucht*, second edition, Vienna.
——, and Isaac, S. (1927). *Die Zuckerkrankheit*, Berlin.
Ross, C. W. (1938). *Arch. Dis. Childh.*, **13,** 289.
Svensgaard, E. (1931). *Acta paediatr., Stockh.*, **12,** Suppl. 4.
Thaysen, T. E. H. (1932). *Non-tropical Sprue*, London.
Torday, A. (1927). *Wien. klin. Wschr.*, **40,** 1263.
Tunbridge, R. E., and Allibone, E. C. (1940). *Quart. J. Med.*, **9,** 11.

CASE REPORT

BRONCHO-PNEUMONIA IN A CRETIN BEFORE AND AFTER TREATMENT WITH THYROID

BY

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Owing to the lowered general metabolism, a hypothyroid person, whether suffering from cretinism or myxoedema, would be expected to react to an acute infection in a subnormal fashion, and it is generally recognized that this is what actually occurs. Rarely, however, can it be possible to witness an acute infection attacking an individual, first in the hypothyroid state and then once more after metabolism has been restored to normal. The following case is an example of such an occurrence.

Case report

J. H., female, aged eleven months, was admitted on February 2, 1940. There were no previous illnesses and nothing relevant in the family history.

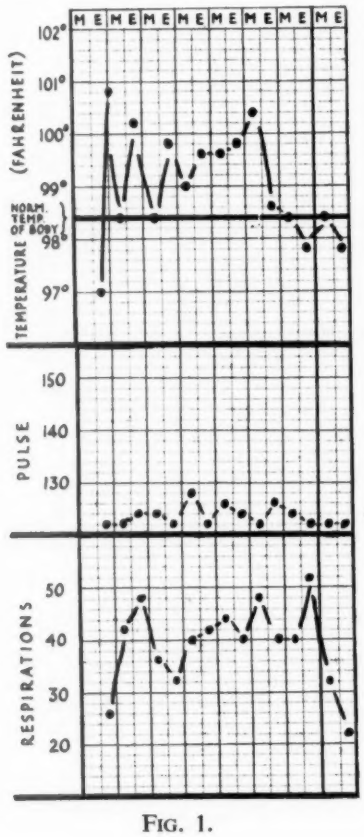
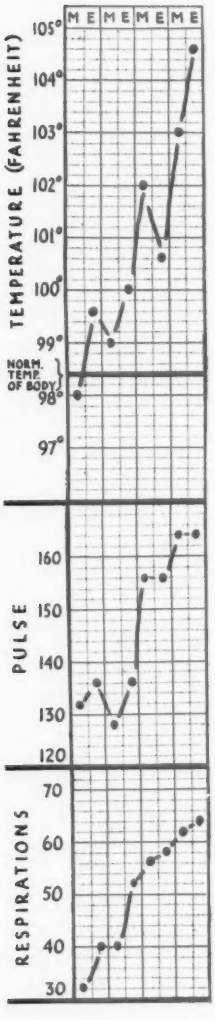


FIG. 1.

FIG. 2.

Birth had been normal, birth weight 8 lb. 1½ oz. Breast feeding was carried out for the first six months, following which the infant had been given a full cream dried milk mixture. Feeding had been extremely difficult owing to lack of interest, and the weight on admission to hospital was only 13 lb. A week previous to admission the baby had developed a common cold, but the general condition had remained good for several days and then deteriorated with the development of vomiting, diarrhoea, cough and rapid bubbling respirations.

On examination the infant was moderately ill, with some cyanosis, alae nasi working and an expiratory grunt. Physical examination of the chest revealed extensive areas of consolidation affecting the upper and middle zones of the left lung and the lower zone of the right lung, and it was evident that a severe broncho-pneumonia was present. Despite the extent of the pulmonary lesions the temperature and respiration rates, and especially the pulse rate, remained at a comparatively low level (see fig. 1), and it was thought that this striking feature could be accounted for by the fact that the infant was evidently a cretin, presenting typical facies (see fig. 2), broad large tongue, coarse dry skin and hair, short square neck with supra-clavicular pads of fat, stumpy thick-set trunk and short limbs, a widely patent anterior fontanelle, no teeth, protuberant abdomen and umbilical hernia.



Treatment was given along the usual lines, including sulphapyridine, oxygen tent, and two-hourly feeds alternating half strength normal saline and boiled cow's milk. As can be seen from fig 1, there was never any respiratory embarrassment, the fever remaining at a moderate level, as did the pulse rate, and the whole condition resolved satisfactorily.

The cretinism responded in the usual way to thyroideum B.P., starting with ¼ grain daily and gradually increasing the dose, and as this took effect feeding became easier each day until eventually after three weeks the infant was on a full mixed diet and had been entirely weaned from the bottle.

A few days later, when about to be discharged she developed another cold, followed by bronchitis and the physical signs of broncho-pneumonia. This time the response was the usual one seen under the age of one year and in striking contrast to the previous attack, namely a steadily mounting temperature, pulse and respiration rate (fig. 3). The same treatment was instituted as on the previous occasion, but without avail, and the illness proved fatal within a few days.

Summary

A case is recorded of a cretin aged eleven months, suffering from severe broncho-pneumonia and reacting subnormally; after resolution, and response to thyroid, a further attack of broncho-pneumonia ensued, producing the usual severe reaction, which ended fatally.

GARGOYLISM

A REVIEW OF THE PRINCIPAL FEATURES WITH A REPORT OF FIVE CASES

BY

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WITH AN ADDENDUM REPORTING AN ADDITIONAL CASE OF GARGOYLISM

BY

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The illuminating work of several authors during the last decade has led to a more general recognition of this rare familial syndrome. Briefly, the disease is a form of congenital chondro-osteodystrophy in which the deformities of the head, trunk and limbs are associated with mental defect, corneal clouding and hepatosplenomegaly. Owing to the uncertain pathogenesis, 'Gargoylism,' the colloquial term introduced by Ellis, Sheldon and Capon (1936), would appear preferable to the numerous other designations which have been suggested. It has become generally accepted in this country, but 'Hurler's Syndrome,' 'Polydystrophy—Hurler Type,' 'Chondro-osteodystrophy—Hurler Type' and 'Dysostosis Multiplex—Hurler Type,' amongst others, are terms usually preferred by continental authors. The impressions resulting from a survey of the literature have been embodied in a short account of the principal features of the disease. Records of fifty-seven cases have been found, although satisfactory details are lacking in nine instances. Doubtless, a number of cases will have been missed owing to the lack of a standardized nomenclature. A further five cases are now presented.

This paper is intended primarily as a tribute to the late Dr. John Thomson of Edinburgh, who was probably the first to recognize the condition as a disease sui generis. Four of the five cases now presented were under his care at the Royal Edinburgh Hospital for Sick Children, the first of the McL. trio as long ago as 1900. When a younger sibling with similar features came to his notice in 1908 he realized he was dealing with a disease which had no counterpart in the literature and called it 'Johnny McL——'s disease' after the first case. It is a pity he did not report these cases, as he would have been the first to draw attention to the disease and would have advanced its more general recognition

by a generation, but it was typical of the man to refrain from publishing work which he considered immature. It is of interest to recall, however, that Dr. Thomson demonstrated the fourth case of this series at a meeting of the Edinburgh—Glasgow Paediatric Club in 1924, when he also gave an account of the salient features of the disease.

Cases reported in the literature

Adequately authenticated cases have been reported as follows:

YEAR	AUTHORS	NO. OF CASES
1907	Berkhan	1
1917	Hunter	2
1919	Hurler	2
1921	Jewesbury and Spence	1
1924	Nonne	3
1925	Putnam and Pelkan	1
1931	Helmholz and Harrington	4
,,	Ruggles	3
1933	Binswanger and Ullrich	2
1934	Sheldon	1
,,	Ellis	1
,,	Poynton, Lightwood and Ellis	1
,,	Davis and Currier	2
,,	Jansen	1
1935	Cockayne	1
1936	Cockayne	2
,,	de Lange and Woltring	2
,,	Ellis, Sheldon and Capon	4
1937	Ellis	1
,,	Bokkel Huinink	1
,,	Liebenam	1
,,	Ashby, Stewart and Watkin	1
,,	Nordmann	2
1938	Ellis	1
,,	Kressler and Aegerter	1
,,	Bindschedler	2
,,	Slot and Burgess	1
1939	Engel	2
1940	Gillespie and Siegling	1

Inadequately authenticated cases have been reported as follows:

YEAR	AUTHORS	NO. OF CASES
1931	Helmholz and Harrington	2
1934	Davis and Currier	1
1936	Ellis, Sheldon and Capon	2
1937	Ashby, Stewart and Watkin	2
,,	Tombleson	1
1939	Höra	1

There is little doubt of the validity of these cases, but the data are insufficient for their inclusion in a review.

The work of Ellis, Sheldon and Capon (1936), who reviewed the literature along with their own series of cases and analysed the clinical features of the disease, constitutes a noteworthy milestone. Ashby, Stewart and Watkin (1937), in the following year, were the first to describe the pathology, their account of the neuropathology being admirable. The full pathological report by Kressler and Aegerter (1938), a year later, was a valuable contribution, as they were the first to demonstrate widespread extracerebral deposits of lipoid

in a typical case of the disease. In addition to the above, the literature has been reviewed by the following authors: Liebenam (1937), Ellis (1937b), Bindschedler, Rodier and Heintz-Bertsch (1938) and Engel (1939). Several of the cases mentioned in this paper have not been included in previous reviews.

Clinical features

Bone changes and general appearance. Growth is usually retarded from an early age. Most of the cases were said to have grown normally for the first year. Liebenam's (1937) patient is of particular interest in this respect, as her twin sister was normal. The mother first noticed a slowing down in the rate of growth at the age of two-and-a-half years; at six to seven years growth ceased. Dwarfing is always severe in those which survive childhood.

THE HEAD. The cranium is nearly always enlarged and, unlike the face, its conformation is variable. Scaphocephaly is the principal type, while brachycephaly is almost as common. Bulging of the squamous part of the temporal bones often occurs and oxycephaly is occasionally found. Hydrocephalus is a frequent complication. Bony ridges along the suture lines and unduly prominent supra-orbital ridges sometimes occur. Closure of the anterior fontanelle is always greatly delayed.

The grotesque facial appearance is typical and one of the most constant features of the disease. The nasal bridge is flat and wide and the nostrils are often turned forwards. The mandible is frequently broad and heavy and the teeth widely spaced, irregular and poorly developed. Dentition commenced at the normal time in about half of the cases, but in others was greatly delayed. The lips are usually thick and the large tongue, often fissured, lies well forward in a slightly open mouth, sometimes actually protruding a little. Full cheeks are the rule and they often have a ruddy hue. The ears usually appear to be unduly low-set and occasionally are enlarged. Coarse, dark eyebrows frequently add to the uncanny appearance, but the hair is usually fine and silky.

The sella turcica was radiographed in about half of the cases and with a few exceptions was considerably enlarged though relatively shallow.

THE TRUNK. The neck is usually short, the head appearing to be planted on the shoulders. The chest is seldom well formed, but gross malformations such as occur in Morquio's disease have not been observed. Flaring of the costal margins and minor degrees of pigeon-breast are frequently seen. X-rays show considerable broadening of the ribs. Dorsolumbar kyphosis is seldom absent and is caused by a dysplasia of one or more of the upper lumbar vertebrae. The affected vertebrae are notably small, with a flattened or wedge-shaped body which frequently bears an anterior hook-like process (see Addendum, fig. 3).

The abdomen is usually enlarged, often grossly. Umbilical hernia is present in the majority of cases and inguinal hernia is common.

THE LIMBS. The most conspicuous features are the relatively short arms and impaired mobility of the joints with slight permanent semiflexion. This impaired movement gives these patients an ungainly and sometimes a slightly crouching attitude and a stiff, clumsy gait. The scapulae usually lie abnormally high and Engel (1939) believes that Sprengel's deformity is a characteristic

feature of the syndrome. Movement at the shoulder is very restricted on abduction of the arms, the scapulae being rotated into the axillae. The broad, short claw-hands are conspicuous. In the legs coxa valga, genu valgum and pes planus have been observed on several occasions.

The radiological changes are more striking in the limbs than elsewhere. The bones are thickened and roughly formed, the latter being most apparent in the neighbourhood of joints. The humeral and femoral heads are irregular and flattened and the glenoid fossae and acetabula unduly shallow. Irregular epiphyseal ossification is a constant feature, osteosclerotic and rarefied patches often being seen. Carpal ossification is retarded.

MENTAL DEFECT. Amentia is one of the most characteristic features of the disease. The majority of the published cases were severely defective. Nine cases gave an impression of normality (Hunter, 1917; Nonne, 1924; Cockayne, 1936; Liebenam, 1937; Orr-Ewing cited by Ashby et al., 1937) and three others of only very slight mental impairment (Hunter, 1917; Davis and Currier, 1934). The three sisters described by Nonne were all 'among the best' at school. Two of these girls were twins. The thirteen-year-old girl described by Liebenam displayed more than average intelligence at school and did as well as her normal twin sister, but unlike the latter, who was jolly and sociable, she was serious, shy and sensitive.

In several instances a falling off in the rate of mental development was observed after the first year or two of life, and at a later stage dementia occurred in a few cases. Fits are not a feature of the condition.

Corneal clouding. This is another salient feature, but it is not invariably present. The clouding is usually congenital and diffuse, giving the corneae a ground-glass appearance, but seldom involves the superficial layers. Occasionally there are multiple discrete opacities. Hitherto, corneal clouding has been regarded by most authors as an essential criterion in the diagnosis of this disease. It did not occur in the cases described by Cockayne (1936) or in those by Hunter (1917) and Nonne (1924). Although no corneal clouding was noted in the second case described by Ashby et al. the neuropathology was typical of the disease and, as the state of the pupils was mentioned, it is unlikely that any corneal clouding could have been missed. Buphthalmos occurred in a few of the cases. It was a feature of the two brothers described by Davis and Currier (1934), who also suffered from optic atrophy and were almost blind.

Hepatosplenomegaly. Enlargement of the liver and spleen occurs in the majority of cases and occasionally is extreme. It does not occur in all cases, however, as demonstrated in the two autopsies reported by Ashby et al.

Other features. Rhinitis, resulting from the nasal malformation, occurs in the majority of cases and recurrent mucopurulent rhinorrhoea is often profuse. Recurrent otorrhoea and respiratory catarrh are common secondary disturbances. Deafness was noticed in several of the more intelligent cases and it may have been an undetected feature in many of those with severe amentia. The muscles are poorly developed and weak. Hypertrichosis is a common feature. A rather leathery skin occasionally occurs. Retarded sexual development was a feature in four of the five cases which had passed the age of puberty

and was still apparent at the age of twenty-three years in the twins described by Nonne (Cockayne, 1936). Congenital malformation of the heart was detected in two cases, and spina bifida, club-foot and cervical rib were each recorded on one occasion. Engel (1939) in his two cases found a considerable decrease in the basal metabolic rate and hypothalamic dysfunction was revealed by the impairment of water secretion as estimated by Hoff's functional test.

In both families described in this paper the affected infants were much larger at birth than their healthy siblings. Other authors have also drawn attention to this fact. Death usually intervenes before the age of ten years, but several of the recorded cases lived longer and two survived for more than twenty years. The period of survival is usually longer in the formes frustes of the disease.

Opportunities for studying subjective phenomena rarely arise owing to the high incidence of mental defect. The principal complaints of Liebenam's patient, whose twin sister was normal, were as follows: difficulty in moving most of the joints, especially in bending down, going upstairs, raising arms to the horizontal and chewing hard food; pains in the back and supra-orbital headache; poor sight and recurrent hearing disturbances; tiredness and dizziness; breathlessness on slight exertion.

Case reports

The McL. family. The parents are now both aged sixty-four years and appear to be healthy. There is no consanguinity. The father is the second of eleven children ; the tenth, a girl, did not walk until she was three years of age, but this may have been due to rickets, as she did well at school; the other siblings were normal. The mother is the eldest of eleven children all of whom were apparently normal. So far as the parents are aware, none of their nieces or nephews resembled their own abnormal children, nor are they aware of a similar condition ever having occurred in the family before. There were nine children, as follows:

	1	Male.	Healthy. Killed in action, aged twenty-two years.
	2	Male.	Died, ? cause, aged six weeks.
	3	Female.	Healthy and married. Died, ? cause, aged twenty-two years. A female child died of ? tuberculosis, aged nine years.
Case 1.	4	Male.	Died aged five years.
	5	Female.	Healthy and married. Has had two children, a girl who died of scalds aged three years and a healthy boy aged three years.
Case 2.	6	Male.	Died aged six years.
	7	Female.	Healthy; aged thirty-two years. Married recently.
Case 3.	8	Female.	Died aged seven years.
	9	Male.	Healthy; aged twenty-seven years. Unmarried.

The three abnormal children were all big babies at birth and much larger than the healthy ones.

Case 1. Johnny McL. was admitted to the Royal Edinburgh Hospital for Sick Children on October 27, 1900, aged two-and-a-half years. He died aged five years.

HISTORY. Birth was spontaneous. The child was breast fed; he never learned to stand by himself nor to crawl. Speech never developed beyond baby talk. He could eat a biscuit, but never learned to use a spoon or cup. He was always doubly incontinent. He recognized his own family. No mental deterioration was observed before death. A few fits occurred between the ages of six and twelve months. Teeth were not unduly late in erupting; many soon decayed. The parents first noticed corneal clouding at about three years old, 'something like cellophane came across the eyes'; this persisted until death, but was not always noticeable. 'Legs were always as thin as straws.' 'He gradually wasted and sank.'

PHYSICAL EXAMINATION (aged two-and-a-half years). Not very detailed, as principal case record not available. A dwarf with a large head and a prominent abdomen. Shape and size of cranium not stated. Nasal bridge flat; a heavy breather with a chronic nasal discharge. Cheeks plump. Neck very short. Pigeon-breasted, with splayed out costal margin. Dorsolumbar kyphosis of moderate degree. No data regarding hands or mobility of limbs. Eyes not mentioned. Abdomen protuberant, with an umbilical hernia and large bilateral inguinal herniae; no reference to liver or spleen.

FIG. 1.—CASE 2. C. McL., aged 3½ years.

Case 2. Charles McL. (fig. 1) was admitted to the same hospital on June 8, 1908, aged three-and-a-half years. He died aged six years.

HISTORY. Birth was spontaneous; the child was breast fed for eighteen months. 'Up to one year was a thriving baby, after that failed to develop as expected.' Walked with the aid of a chair pushed in front of him at three years old, but never walked alone, usually crawled. Speech never developed beyond baby talk. 'When hungry points to the dresser, when thirsty to the well.' Always doubly incontinent. Good tempered. Mentality developed further than in case 1, 'he was a shade cleverer.' No mental deterioration was observed.

Teething began at nine months, when there was one convulsion; many of the milk teeth decayed early. Parents noticed a corneal haziness which was similar to that seen in case 1. The child suffered from recurrent nasal discharge and otorrhoea from early infancy. He gradually became very emaciated before death.

PHYSICAL EXAMINATION (aged three-and-a-half years). A dwarfed child weighing 26 lb. Head large, circumference 20½ in.; fontanelle open, area ½ sq. in. Nose broad, constant mucous discharge. Mouth open, with tongue well forward. Cheeks plump. Neck very short. Thorax narrow and pigeon-breasted. Marked dorsolumbar kyphosis. Hands stumpy, with short broad fingers. Sits up in bed with legs crossed and has a vacant expression. Ruddy complexion; skin rather leathery. Eyes appear normal. Abdomen very prominent, with large umbilical hernia and wide diastasis of the recti muscles. Liver palpable one finger-breadth below the costal margin and spleen palpable at costal margin. Mild bronchitis.

Case 3. Jenny McL. was admitted to the same hospital on July 12, 1913, aged two years and three months. She died aged seven years.

HISTORY. Birth was spontaneous. Breast fed for eight months. 'A fine plump baby up to a year, after which did not seem to grow until shortly before admission.' Never learned to walk, but crawled about the house. Unlike the two brothers, learned to say a few intelligible words. Learned to use a spoon and cup. Always doubly incontinent. 'Cleverer than the two brothers.' No mental deterioration was observed. Never had fits. Teething began at seven months, but many of the milk teeth decayed early, as in the case of the two boys. No haziness of the eyes was observed by the parents in this case and she was not seen again in hospital. She snored a great deal, and had occasional otorrhoea.

PHYSICAL EXAMINATION (aged two years three months). A dwarfed child weighing 21¼ lb. Head 'normal shape,' circumference 19½ in., fontanelle still open. Nasal bridge broad and sunken. Upper lip prominent. Mouth usually closed, but tends to suck tongue. Ears rather large. Neck short. Chest shows tendency to pigeon-breast with sternum thrown well forward. Slight dorsolumbar kyphosis. Fingers stumpy, particularly the thumbs.

A quiet child; can be induced to smile occasionally. Complexion ruddy; skin rather leathery. Eyes appear normal. Abdomen slightly prominent, with small umbilical hernia. Liver enlarged, with lower border three finger-breadths below costal margin in midclavicular line. Spleen greatly enlarged, with lower border extending four finger-breadths below the costal margin. Heart enlarged with loud basal murmur indicating congenital malformation. X-ray examination of sella turcica failed owing to movement.

The N. family. The parents are first cousins, their mothers being sisters. They are healthy. The mother has seven sisters and one brother, all of whom are healthy and married; they all have families of three to five children who are also healthy. The father is also one of nine children; he has a twin sister with four healthy children, another sibling has one child, four others are married but childless, and two are unmarried. The parents were not aware of abnormal children such as their own ever having occurred in the family before. There were four children as follows:

CASE 4.	1	Male.	Died aged six years and four months.
	2	Male.	Healthy; aged seventeen years.
	3	Female.	Healthy; aged thirteen years.
CASE 5.	4	Female.	Died aged eight years and four months.

The two abnormal children were big babies and weighed 9½ lb. at birth, whereas the two normal babies weighed 8 lb.

Case 4. James. N. (fig. 2 and 3) was examined at Royal Edinburgh Hospital for Sick Children on June 1, 1921, aged one year and seven months. He died aged six years and four months.

HISTORY. The child was born spontaneously and was breast fed for one year. The parents were not concerned about the child until the age of six months, when they were struck by the large size of the head and angulation of the lower spine. There seemed to be little growth after the third year. The

FIG. 2.—CASE 4. J. N., aged 1½ years.

FIG. 3.—CASE 4. Profile of J. N., aged 1½ years.

child was slow in learning to smile and grip objects. He began to walk at two years, but ceased to do so twenty months before death. He never spoke more than a few words, such as 'motor' and 'horsey,' and called mother 'Terry.' He began to feed himself in the third year, but ceased to do so one year before death. Habits became semi-clean in the third year, but he relapsed about two years before death. He knew where to go for food and drink, and recognized his own family and their friends, but cried when strangers entered the house. Mental deterioration became more pronounced in the last six months of life. He never had any fits.

Teething was greatly delayed and slow, the first two teeth not erupting until well over one year old. Many of the teeth soon decayed. Corneal clouding was first observed at a little over one year old. The brachial stiffness seemed to get worse as time went on. The abdomen was always large. The inguinal hernia was cured by operation at three-and-a-half years. The tongue always protruded from the open mouth and was enlarged and fissured. There was an almost continuous rhinorrhoea, but never any otorrhoea. He spent the last eight months of life in an institution, where he died of 'double pneumonia' aged six years and four months.

PHYSICAL EXAMINATION (aged one year seven months). The head is considerably enlarged and the fontanelle still large. Root of nose flat and broad.

Cheeks plump. Jaw broad and rather heavy. Neck short, the head appearing to be planted on the shoulders. Thorax shows considerable degree of pigeon-breast and flaring of the costal margins. Dorsolumbar kyphosis of moderate degree. Arms short, the stumpy hands being noticeable owing to their semi-flexed fingers. Movement at shoulder joints very limited, abduction of arms rotates scapulae into axillae. The child is able to sit up, but the large head is held unsteadily. Both corneae show hazy, ground-glass appearance. The hair is light brown and silky, and the eyebrows bushy; there is hypertrichosis on the upper part of the back. The abdomen is very large, with a large umbilical hernia and a unilateral inguinal hernia. Liver considerably enlarged and spleen very much so, extending almost three finger-breadths below costal margin.

Case 5. Muriel N., was examined at the same hospital on March 27, 1929, aged one year and one month. She died aged eight years and four months.

HISTORY. Birth spontaneous, child was breast fed for seventeen months. Parents first became alarmed at about eight months, when they noticed haziness of the eyes. When called in at that time the family doctor at once recognized the child's close resemblance to case 4. There was little growth after the first three years, ' fair until then.' The child was slow in taking notice and gripping, and was two years old before she could feed otherwise than by bottle. She began to creep at two years, but never learned to stand nor walk; she could ' run like a hare ' on her knees, but ceased to move about ' after a fall ' when five years old. Never spoke a word, nor learned to feed herself. Always double incontinence. Like her brother, she knew her family and was afraid of strangers, but in general the boy was ' the sharper of the two.' The mental state deteriorated during the last three years of life. Never any fits. Teething was greatly delayed, and many of the teeth soon began to decay. The limbs were always very thin. There was chronic snuffles and rhinorrhoea. Mouth was often open, but the tongue not protruded; ' it was rough and rather large.' Ultimately the child became very emaciated, but continued to feed well until she died in sleep, aged eight years and four months. When last seen, two weeks before death, she was extremely weak and emaciated.

PHYSICAL EXAMINATION (aged one year and one month). Head somewhat enlarged, with prominent frontal eminences; anterior fontanelle still large. No teeth. Unable to sit up. Considerable corneal opacity present in both eyes. Liver enlarged, extending two finger-breadths below costal margin, and spleen very large, reaching fully three finger-breadths below costal margin. Apart from the absence of an inguinal hernia and of hypertrichosis, the clinical features were similar to those already described in the case of the brother.

Pathology

Post-mortem examinations were made on only four of the cases reported in the literature. Unfortunately, the diagnosis was unknown at the time in each one and consequently the investigations were incomplete. Kressler and Aegerter, in the last of these cases, furnished the most complete report, but they regretted their failure to carry out biochemical analyses on the fresh tissues.

Tuthill (1934) was the first to describe the autopsy findings in a case of this disease. The case was one of those reported by Hurler (1919), but he was unaware of this fact and thought the neuropathology typical of the juvenile type of amaurotic family idiocy which was regarded as having unique histological features at that time. The more recent observations of Ashby et al. (1937) and of Kressler and Aegerter (1938) corresponded with those of Tuthill and firmly

established the fact that the neuropathology of this disease closely resembles that of the juvenile form of amaurotic idiocy. The extreme ballooning of nerve cells and the marked degeneration of their processes which occur in the infantile form of the latter disease were not seen in any of these cases.

A brief account of the principal pathological features as seen in the few reported autopsies will be given below.

The brain. The morbid conditions in the brain were almost identical in all four cases. The convolutional pattern was rather simple. Internal hydrocephalus was found in Tuthill's case.

The cortical nerve cells were sparse, and degenerative changes in the nerve cells were seen throughout the central nervous system. Many were swollen and displayed eccentric nuclei with greatly diminished Nissl substance and conspicuous masses of lipoid matter deposited in the cytoplasm. While occasional disintegrating nerve cells were seen, others showed little, if any, departure from the normal, but appropriate staining methods seldom failed to reveal the presence of the abnormal lipoid deposits. The cell processes were unaltered in the cases of Ashby et al., but some thickening was observed by Kressler and Aegerter. Degenerative changes were more pronounced in the basal ganglia and in the brain stem than in the cortex. Profoundly altered cells were particularly numerous in the optic thalamus, the midbrain, the dentate nucleus, the inferior olives of the medulla and the ventral horns of the spinal cord; but in the optic thalamus the granular deposit in the large cells was coarser and more conspicuous than elsewhere. In the cortex the deeper cell layers were the more severely affected, particularly the medium and large pyramidal cells. Ballooning of the cells was a feature in the prefrontal areas. Unlike Tay-Sach's disease, the cerebellar changes were, for the most part, only slight. Gliosis was a conspicuous feature in the optic thalamus and in the hypothalamus and, to a lesser extent, in the periventricular regions. Elsewhere the increase of glial tissue was only slight.

An extracellular lipoid infiltration was found in certain areas of grey matter, but none was seen in the white matter. Its distribution was principally perivascular and the heaviest deposits were seen in the globus pallidus. Deposits were also seen in the putamen, the caudate nucleus, the optic thalamus, the midbrain and the dentate nucleus. Cortical deposits were confined to the precentral and postcentral areas, and small amounts were also seen in the cerebellar cortex.

The bones. The morbid anatomy of the bones has been mentioned under x-ray appearances. Histological examination of the epiphyseal cartilage has been reported on only two occasions. Kressler and Aegerter found normal ossification and healthy bone growth in their case, and although there were lipoid deposits in most of the tissues, none were found in the bones. Recently, however, Höra (1939) and Elsner, working in Pfaundler's Clinic at Munich, demonstrated histologically a hypoplastic chondrodystrophy in the bones of an affected infant.

Other tissues. Kressler and Aegerter found a widespread lipoid infiltration of the tissues in their case. It was both intra- and extracellular in most situa-

tions. The heaviest extracerebral deposits were found in the liver, the anterior lobe of the pituitary gland and in the lymph glands, but large amounts of lipoid were also seen in the myocardium and pericardium, the lungs and pleurae, the thymus, the spleen, the testes and the corneae. In the corneae proper the lamellae were widely separated. While pointing out that this might have been an artefact, the author thinks that the spaces were more likely to have been occupied by lipoid matter which had been dissolved out during fixation. There was no evidence of any other pathological process in the corneae. No deposits were seen in the thyroid, the pancreas, the suprarenals, the kidneys, the bones or the bone-marrow.

In addition to the brain Ashby et al. examined the thyroid, the pituitary, the thymus and the suprarenals in their first case and the thyroid and liver in their second case. There was no sign of lipoid deposition in any of these tissues. In neither case was there any hepatic or splenic enlargement. Ellis (1937b) failed to find any evidence of lipoid infiltration in a biopsy examination of the liver and spleen of a typical case with enlargement of these organs.

The anterior lobe of the pituitary gland was considerably enlarged in the two cases in which it was examined. There was a hyperplasia of all three types of cell in both instances, but lipoid infiltration was seen in only one case. It was abundant, and both intra- and extracellular, the largest deposits being seen in the chromophobe cells. The large size of the sella turcica in most of the cases suggests that enlargement of the pituitary gland usually occurs, although the enlargement of the sella may be a manifestation of osseous dysplasia, as suggested by other authors.

The thyroid gland was examined in three cases and it was found to be abnormal in two. In both these cases the structure was consistent with hypothyroidism, one having a foetal structure and the other showing a considerable degree of parenchymatous degeneration and fibrosis. Patients suffering from this disease resemble cretins in a number of ways and not infrequently are diagnosed as such. Several of the reported cases were given courses of thyroid therapy, but they all failed to show any appreciable improvement.

The lipoid deposit. The properties of the lipoid deposits in the brain of their first case were carefully investigated by Ashby et al. They found that the staining reactions of the intracellular and the extracellular deposits were different, those of the intracellular substance having a close resemblance to the staining reactions of the lipoid found in the juvenile type of Tay-Sachs' disease. This intracellular deposit stains with scharlach red in both diseases, but the extracellular only in Tay-Sachs' disease. They also found that the staining reactions and the solubilities of the extracellular deposit failed to correspond with those of any known lipoid, and regretted that it was not present in sufficiently large amounts to permit of its isolation. On the basis of the solubility tests they believed they were dealing with a lipoid consisting mostly of cerebrosides, chiefly phrenosin and kerasin.

The staining reactions of the infiltrating substance in the case reported by Kressler and Aegerter did not correspond with those found in the case of Ashby et al. They were almost consistently negative.

Comment. Ellis et al. (1936), in discussing Tuthill's findings, were the first to suggest that gargoylism might ultimately prove to be a disorder of lipoid metabolism. This belief appeared to be substantiated by the admirable work of Ashby et al. in the following year. They demonstrated a neuropathology similar to that of Tay-Sachs' disease which was first recognized as a lipoidosis only a few years earlier. The demonstration of widespread extracellular lipoid deposits by Kressler and Aegerter in their typical case appeared to confirm the view that this disease also belongs to the lipoidosis group. There need be no difficulty over the fact that extracerebral lipoid deposits were not found by Ashby et al. in their cases, as variability in the distribution of the lipoid deposits is a characteristic feature of the lipoidoses. The failure of Kressler and Aegerter to confirm the observations of Ashby et al. on the nature of the lipoid may be accounted for by the different methods of fixation employed.

The extracerebral pathology of the disease, apart from the osseous anomalies, cannot be envisaged in its true perspective until more necropsies have been performed. Further, ante-mortem diagnosis should afford opportunities, which have not arisen hitherto, for adequate biochemical analysis of the lipoid deposits.

As suggested by other authors, it seems likely that endocrine dysfunction may contribute to the clinical picture of the disease. The important rôle played by the hypothalamus in metabolic processes has become increasingly evident in recent years. It is acknowledged to play a part in lipoid metabolism, and one wonders what significance the gliosis in that region may have in these cases. The hypothalamic disturbances are probably connected with the changes seen in the pituitary and thyroid glands and these, in turn, with some of the clinical features of the disease such as the chondrodystrophy and dwarfism. However, Ellis's (1937b) remark that ' it is as yet too early to assess the part played by the thyro-pituitary mechanism in the production of the syndrome ' is still applicable.

Etiology

Although males predominate there is no significant difference in the sex incidence. The available evidence indicates that the condition is recessively inherited. A cousin of the boy reported by Jewesbury and Spence (1921) was similarly afflicted and five instances of consanguinity in the parents have been recorded. The parents in the last two cases of this series were first cousins, as in an unpublished case mentioned by Cockayne (1936), while the parents of the three sisters described by Nonne (1924) and in one of the cases published by Binswanger and Ullrich (1933) were second cousins. The paternal grandparents of the two brothers recorded by Hunter (1917) were first cousins.

The occurrence of the disease in a pair of siblings has been recorded on nine occasions as follows: Hunter (1917), Helmholz and Harrington (1931), Ellis et al. (1936), Cockayne (1936), de Lange and Woltring (1936), Bindschedler (1938), Engel (1939) and cases 4 and 5 of this series. An unpublished instance was mentioned by Ashby et al. (1937). The disease has been observed in three members of a family on four occasions. Nonne (1924) reported its occurrence in three sisters, two of whom were twins. A sister of the two brothers reported

by Davis and Currier (1934) appears to have been similarly affected. Three siblings in a group of cases described by Ruggles (1931) as examples of Morquio's disease are now regarded as belonging to this syndrome. Finally, the first three cases of this series were all born of the same parents. The five cases of the present series thus belonged to only two families. It is apparent that the disease has a high familial incidence, as this was a feature in thirty-two of the sixty-two cases mentioned in this paper.

The available evidence, though fragmentary, would appear to justify the view of several of the more recent authors that gargoylism should be grouped with the lipoidoses. The other diseases comprising this group are Gaucher's disease, Schüller-Christian's disease, Niemann-Pick's disease and Tay-Sach's disease. In all five conditions the familial incidence is significantly high and it would seem that all are recessively inherited. Further, although some cases of Gaucher's disease and Schüller-Christian's disease may not become manifest until adult life, they all predominate in early childhood and are essentially congenital.

Conclusion

Several of the recorded cases of gargoylism have been regarded as examples of Morquio's disease by their authors. In the latter disease only skeletal changes occur, and whereas the head is normal, the deformities of the trunk and limbs are much more extreme than in gargoylism. There is no mental defect in Morquio's disease. It is not surprising that gargoylism is frequently mistaken for cretinism.

Although a preference has been expressed for the name ' gargoylism,' there are doubtless some who would prefer an eponymic term in accordance with the precedence established in the case of the other lipoidoses. In such an event the name of ' Hunter-Hurler's Disease ' is suggested. Gertrud Hurler, who published an account of two cases from Pfaundler's Clinic at Munich in 1919, is generally regarded as being the first to describe the disease, hence the term ' Hurler's Disease.' It has been overlooked, however, that two years earlier Hunter gave an excellent description of the condition in two brothers, and he pointed out that he regarded it as a new disease to which he could not find any reference in the literature. It is regrettable to confuse the question of nomenclature further, but in the absence of universal standardization it seems justifiable to make this suggestion, not only because of the wish to do honour where it is due, but also for the sake of accuracy.

Summary

A short account of the features of gargoylism has been given.

Fifty-seven cases recorded in the literature have been reviewed. Five additional cases are now presented.

The disease is congenital, and the principal clinical features are chondro-osteodystrophy with extreme dwarfism, mental defect, corneal clouding and hepatosplenomegaly.

The most constant pathological changes are found in the osseous and nervous systems. The bones are thickened and many of them display characteristic deformities. In the brain there are widespread degenerative changes in the nerve cells with intra- and extracellular lipoid deposits. Lipoid deposits may occur in the corneae, liver, spleen and other tissues.

The disease is recessively inherited and there is a high familial incidence. There have been five instances of consanguinity in the parents.

The available evidence, although fragmentary, offers a considerable amount of support for the view expressed by several authors within the last few years that the disease should be grouped with the congenital disorders of lipoid metabolism. The relationship of the chondro-osteodystrophy to the other morbid features is obscure.

Thanks are due to Professor Charles McNeil for the interest he has taken in this work. He was associated with the late Dr. John Thomson for many years and knew all the patients of this series except the first.

References

Ashby, W. R., Stewart, R. M., and Watkin, J. H. (1937). *Brain*, **60**, 149.
Berkhan, O. (1907). *Arch. Anthrop., Braunschw.*, **34**, 8.
Bindschedler, J. J. (1938). *Bull. Soc. Pédiat., Paris*, **36**, 571.
——, Rodier, J. M., and Heintz-Bertsch, Mme. (1938). *Rev. franç. Pédiat*, **14**, 116.
Binswanger, E., and Ullrich, O. (1933). *Z. Kinderheilk.*, **54**, 699.
Bokkel Huinink, A. ten (1937). *Maandschr. kindergeneesk.*, **6**, 449.
Cockayne, E. A. (1935). *Proc. roy. Soc. Med.*, **28**, 1067.
—— (1936). *Ibid.*, **30**, 104.
Davis, D. B., and Currier, F. P. (1934). *J. Amer. med. Ass.*, **102**, 2173.
Ellis, R. W. B. (1934). *Proc. roy. Soc. Med.*, **27**, 1022.
—— (1937a). *Ibid.*, **30**, 158.
—— (1937b). '*Gargoylism*' : *Brit. Encyclopaedia Med. Practice*, **5**, 496.
—— (1938). *Proc. roy. Soc. Med.*, **31**, 770.
——, Sheldon, W., and Capon, N. B. (1936). *Quart. J. Med.*, **29**, 119.
Engel, D. (1939). *Arch. Dis. Childh.*, **14**, 217.
Gillespie, J. B., and Siegling, J. A. (1940). *J. Bone Jt. Surg.*, **22**, 171.
Helmholz, H. F., and Harrington, E. R. (1931). *Amer. J. Dis. Child.*, **12**, 793.
Höra, J. (1939). *Virchows Arch.*, **305** ii, 298.
Hunter, C. (1917). *Proc. roy. Soc. Med.*, **10** i, 104.
Hurler, G. (1919). *Z. Kinderheilk.*, **24**, 220.
Jansen, M. (1934). *Z. orthop. Chir.*, **61**, 253.
Jewesbury, R. C., and Spence, J. C. (1921). *Proc. roy. Soc. Med.*, **14**, 27.
Kressler, R. J., and Aegerter, E. E. (1938). *J. Pediat.*, **12**, 579.
de Lange, C., and Woltring, L. (1936). *Acta Paediatr., Stockh.*, **29**, 71.
Liebenam, L. (1937). *Z. Kinderheilk.*, **59**, 91.
Nonne, M. (1924). *Dtsch. Z. Nervenheilk.*, **83**, 263.
Nordmann, J. (1937). *Bull. Soc. Ophtal. Paris*, **49**, 256.
Poynton, F. J., Lightwood, R. C., and Ellis, R. W. B. (1934). *Proc. roy. Soc. Med.*, **27**, 1025.
Putnam, M. C., and Pelkan, K. F. (1925). *Amer. J. Dis. Child.*, **29**, 51.
Ruggles, H. E. (1931). *Amer. J. Roentgenol.*, **25**, 91.
Sheldon, W. (1934). *Proc. roy. Soc. Med.*, **27**, 1003.
Slot, G., and Burgess, G. L. (1938). *Ibid.*, **31**, 1113.
Tombleson, J. B. L. (1937). *Ibid.*, **30**, 1070.
Tuthill, C. R. (1934). *Arch. Neurol. Psychiat., Chicago*, **32**, 198.

ADDENDUM

REPORT OF AN ADDITIONAL CASE OF GARGOYLISM

BY

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The following case of gargoylism is reported as an addendum to Dr. Henderson's paper, as it illustrates a number of the clinical and radiological features of the condition referred to in the text.

L.C., a girl, aged two years at the time of examination (June, 1940), was born at term by an easy low-forceps delivery. Her parents and grandparents were normal, and no similar condition was known in either family. There was no consanguinity of parents. There had been a previous miscarriage at ten weeks; no other children.

The patient weighed seven and a half pounds at birth; the umbilical cord was said to have been exceptionally large. She was breast fed for three months; breast feeding was discontinued owing to failure of the baby to gain weight after two months old and because of the mother's ' nervous state.' The baby was subsequently reared on dried milk, followed by mixed feeding. She sucked well in spite of severe snuffles and purulent nasal discharge dating from birth. She cut her first teeth at thirteen months of age, and walked alone at twenty-three months. She had been well except for colds and cervical adenitis during the first year. At the time of examination, she had been clean both by day and night for some months. She was feeding herself, holding cup and spoon, and was beginning to talk. She was said to be ' very observant ' and would always go to fetch her father if her mother appeared in a new dress! She was obviously interested in her own clothes, and though frightened of strangers, played normally with her mother and understood simple requests. She recognized friends and animals with which she was familiar.

On examination (June, 1940). The child appears of normal, or almost normal, intelligence for age, though she is intensely resentful of examination by strangers. She is of average height (32½ in.) and weight (27 lb.) for age (fig. 1).

THE HEAD appears slightly larger than normal, but is not obviously hydrocephalic. Circumference 19⅛ in. (average normal 18½ in.). Intermeatal measure (over vertex) 12½ in. The anterior fontanelle is patent. The hair is light brown in colour, and rather thick and coarse. The frontal veins lie in deep grooves in the frontal bones. There are fourteen teeth present.

THE FACIES is typical of the condition, the features having a peculiarly gross and heavy appearance. The lips are large and thick; there are deep naso-labial grooves, heavy cheeks, and depression of the nasal bridge, with profuse purulent nasal discharge. The eyebrows are sparse, coarse and black.

THE EARS are somewhat flattened and set unusually low.

THE EYES show bilateral clouding of the corneae, which though less marked than in many previously recorded cases, prevents satisfactory examination of the fundi. Visual acuity appears moderately good, though accurate testing is impossible.

THE ABDOMEN is distended and there is a small umbilical hernia. The liver is enlarged two finger-breadths below the costal margin, and the spleen is just palpable. Genitalia normal.

SKELETAL SYSTEM. There is an angular kyphosis in the region of the first lumbar vertebra and a deep dimple in the mid-line of the back immediately below it (fig. 2).

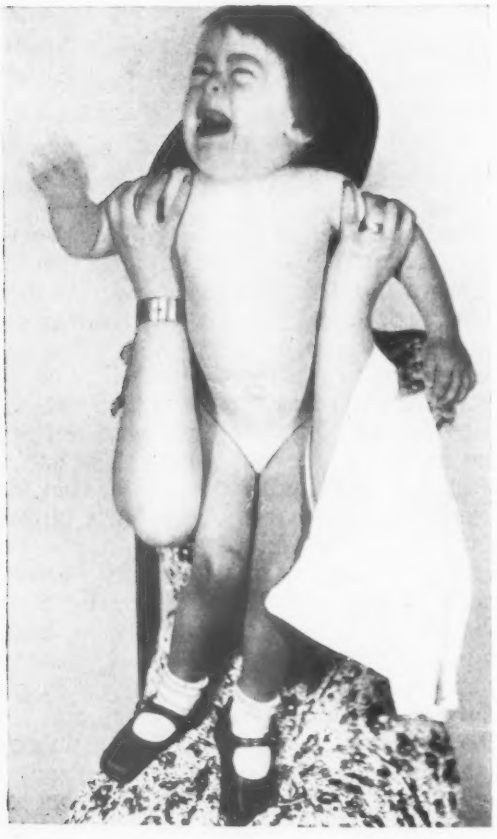

FIG. 1.—L. C., showing facies and characteristic flexion deformity of left hand.

FIG. 2.—Lumbar kyphosis.

The thorax is normal except for slight flaring of the lower ribs. The scapulae are normally placed.

There is some limitation of extension of the elbows, knees and hips, and more marked flexion deformity of the interphalangeal joints of the hands. There is a deep dimple over the head of the radius on either side.

Radiological examination

SKULL. The anterior fontanelle is patent, and the coronal sutures abnormally wide. The sella turcica appears shallow and elongated; the clinoid processes are not clearly defined, but there is no evidence of erosion.

SPINE. The body of the first lumbar vertebra is diminished in size and its upper and anterior portion is defective, giving rise to an angular kyphosis in this region (fig. 3).

RIBS. The lower ribs are expanded anteriorly.

HIPS. Both acetabula are poorly formed (fig. 4), the roof being slanting. The femoral necks are valgoid and there is partial subluxation.

RIGHT SHOULDER. The glenoid fossa is poorly formed, and the head of the humerus flattened.

FIG. 3.—Spine showing deformity of body of first lumbar vertebra and kyphosis. Anterior expansion of ribs.

FIG. 4.—Hips.

FIG. 5. Hands. Widening and irregularity of metacarpals and phalanges.

HANDS. The metacarpals and phalanges show the widening and irregularity of outline characteristic of the condition. The interosseous spaces are increased in size (fig. 5) and the epiphyses small.

Comment

Although the changes are not so marked as in many of the published cases, this patient shows the following characteristic features of gargoylism: the peculiar facies, which in itself is diagnostic; hepatosplenomegaly ; chondro-osteodystrophy, giving rise to flexion deformities, particularly of the hands; defect of the body of one of the upper lumbar vertebrae, resulting in kyphosis; clouding of the corneae; depression of the nasal bridge, with purulent nasal discharge; an elongated sella turcica; low-set ears; and hernia. Minor stigmata which I have also seen in other cases are the deep grooves lodging the frontal veins, and the sparse eyebrows composed of coarse dark hairs. A point in which this child differs from most of the classical cases is in her mentality. This appears almost normal for her age, and though it is too soon to predict that mental deterioration will not occur, the prognosis seems relatively more hopeful. Since the familial incidence of the condition is established, it was necessary to warn the parents that, even in the absence of consanguinity, there was a possibility of a subsequent child being affected.

PROLIFERATIVE MURAL BRONCHIOLITIS

BY

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Bronchiolitis is a condition which occurs predominantly in infants and young children. Although the clinical picture and the grave significance are well known, the morbid anatomy and histology of the condition have been the subject of very little investigation. The anatomical features, as will be shown in a later paper, vary a great deal, there being a continuous gradation from the slightest to the severest forms. Two main groups must be distinguished: **catarrhal** and **mural** bronchiolitis. In the first type the mucous membrane alone is involved, in the second the whole wall is affected. Catarrhal bronchiolitis seems to be less common than mural bronchiolitis. The latter type of inflammation is the usual reaction of the bronchioles to infection.

Mural bronchiolitis appears in many degrees of intensity. It is useful to differentiate three groups: **simple, proliferative** and **destructive** mural bronchiolitis.

SIMPLE MURAL BRONCHIOLITIS means infiltration of the wall and engorgement of the vessels without any lesion or change in the epithelium.

In PROLIFERATIVE MURAL BRONCHIOLITIS infiltration and engorgement is ordinarily intense. In addition, proliferation or pathological growth of the epithelium, of the basal cells and, occasionally, of other elements of the bronchiolar wall or the surrounding lung tissue is characteristic.

The DESTRUCTIVE TYPE is marked by complete destruction of the epithelium and other adjacent constituents of the bronchiolar wall. In these cases the reaction of the surrounding lung tissue is generally more marked.

There is, apparently, no fundamental difference between the three types. It is a matter of degree, probably due to different infective agents or to secondary infections superimposed on the primary agent. Transitions from the one form to the other occur frequently. However, in most cases classification is possible.

This article deals exclusively with proliferative mural bronchiolitis (P.M.B.). This type shows the most characteristic features of the different degrees of mural bronchiolitis. It was first described (although it was called bronchopneumonia) in measles and later it was found also in whooping cough, diphtheria and influenza (Lange, 1901; Jochmann and Moltrecht, 1904; Hart, 1904; Huebschmann, 1917; MacCallum, 1919; Opie, 1921; Feyrter, 1925). Interest in P.M.B. was revived when American authors had to deal with large epidemics of measles and influenza in army camps (MacCallum, 1919; Opie, 1921).

MacCallum has made a study of the pulmonary lesion in the case of measles in the adult and has published his results in a fine monograph. Later the pandemic of influenza produced numerous papers (Opie), showing that the same pulmonary lesion which MacCullum had seen in measles was a common sequel of influenza.

MacCallum gave the condition the name of ' interstitial bronchopneumonia,' observing that interstitial spread originates from the bronchioli. This interstitial spread is not, as will be pointed out later, an essential feature in infants. It will be shown that the condition is characterized rather by intense inflammatory changes throughout the whole bronchiolar wall. Pneumonia (interstitial or otherwise) may follow, but this is a secondary process. It seems advisable to keep these two processes separated.

This paper is only concerned with the primary lesion, which will be shown to be of the proliferative mural type, according to the classification set out above. The chief features of P.M.B. are characteristic. The wall is densely infiltrated with monocytes, a large proportion of which are plasma cells. The vessels of the adventitia are engorged. This infiltration and hyperaemia give rise to an enormous thickening of the bronchiolar wall. These features are common, more or less, to all forms of mural bronchiolitis. In the case of P.M.B. there are the proliferative features superadded which will be described in this paper.

At the time when MacCallum wrote his monograph (1919) no definite cause for ' interstitial bronchopneumonia ' could be found. MacCallum himself came to the conclusion that the condition could be produced by various organisms, pneumococci, staphylococci and, above all, by haemolytic streptococci and the influenza bacillus. Our interest has been aroused by finding P.M.B. in different degrees of intensity in the lungs of a number of infants. None of these had measles or pertussis, nor could they be recognized clinically as influenza. There seemed to be only two possibilities: either they were cases of influenza without distinct clinical symptoms or they were some other condition, unknown up to the present. This might be an infection of unknown kind or a bronchiolar reaction to which no attention had been paid hitherto. A closer investigation appeared worthwhile.

Case reports

Case I. Female, aged two-and-a-half months. History of cough and vomiting of one day's duration. When seen, the infant was very ill and cyanosed. There were signs of consolidation present at the left base, and later consolidation at the right base. A temporary improvement followed treatment, but the infant died after an illness of three weeks. Diagnosis: bronchopneumonia. N.B.: x-ray showed consolidation of both lower lobes.

POST-MORTEM. Fibrinous pleurisy over both lower lobes. Thick yellow pus in the trachea and main bronchi. Typical appearance of bronchopneumonia in both lower lobes. B. Pfeiffer grown from the bronchial pus.

Case 2. Female, aged three months. The birth was normal. Four weeks afterwards the baby was observed to make a whistling noise on breathing. She was frequently cyanosed. She was admitted for investigation. Bronchitis

developed. There was no pyrexia. The general condition became worse. Death occurred after an illness of three to four weeks. Diagnosis: Atelectasis of the left upper lobe.

POST-MORTEM. Thick yellow pus in the trachea and bronchi. Scattered areas of consolidation and collapse were present in the whole of the right lung and the left lower lobe.

Case 3. Male, aged nine months. Since the age of four months the baby had frequently vomited. There was only a slight gain in weight. He was admitted for investigation. The vomiting continued and the infant became dehydrated. A cough developed. Later signs of bronchopneumonia appeared. The infant died after an illness of two to three weeks.

POST-MORTEM. Both lower lobes were solid, due to a combination of collapse and broncho-pneumonic infiltration. The other lobes were over-distended.

Case 4. Female, aged thirteen months. This was a typical case of coeliac disease with characteristic fatty stools. Soon after admission, broncho-pneumonia developed and the infant died after an illness of two weeks' duration.

POST-MORTEM. Pus was present in both middle ears. There was a confluent type of broncho-pneumonia in the left lower lobe and a patchy infiltration of all the other lobes.

Case 5. Female, aged eight months. The infant was a mongol. For several days she had had nasal catarrh. The day before admission she was feverish and started to cough. Dyspnoea was present. On admission, the infant was moribund. She was cyanosed and had grunting respirations. There were signs of consolidation in both lower lobes. Death took place shortly after admission. Diagnosis: broncho-pneumonia.

POST-MORTEM. Heart: there was a large deficiency in the inter-auricular septum; this was the only congenital lesion. Lungs: there were solid areas in both lower lobes and the apex of the right upper lobe.

Clinical aspects

It will be seen from the case reports that there is nothing in the clinical appearances of these cases to distinguish them from cases of broncho-pneumonia, whether of the primary type or of the kind following or complicating some pre-existing disease. In two of the cases (1 and 5) the onset was sudden and the patients became rapidly toxaemic, with severe respiratory embarrassment. The first case died after an illness of three weeks' duration, the latter after one of only two to three days. Cases 3 and 4 were infants who were extremely wasted, the one from persistent vomiting, the other from coeliac disease. They developed ' broncho-pneumonia ' while in hospital and died after short illnesses of about two or three weeks' duration.

Case 2 was diagnosed as atelectasis. Although there was evidence of consolidation of the lung, there was no pyrexia at any time during the course of the illness. At autopsy, however, there was definite consolidation of both lungs associated with collapse.

The histological picture

The general impression of the microscopical picture is that of bronchiolitis combined with collapse. In view of the macroscopical appearance one would have expected to find broncho-pneumonic foci. However, the macroscopical

appearance of broncho-pneumonia is only due to the enormous thickness of the inflamed wall.

The lung tissue in the area affected by bronchiolitis is, as a rule, collapsed, but the air-spaces are not infiltrated nor is the interstitia. Some desquamated cells are frequently seen within the air-spaces. Fibrin is absent.

Thickening of the bronchiolar wall is, in the first place, produced by dense infiltration with monocytes. Many of them are plasma cells. The blood vessels of the wall are strikingly engorged. This contributes a great deal to the thickening of the part of the bronchiolar wall external to the elastic layer.

The bronchiolar wall consists of two chief parts, which are separated by the elastic sheath external to the epithelium. There is, however, an almost imperceptible layer of cells interposed between the elastica and epithelium. It consists normally only of a few oblong, spindle-shaped cells; whether they form a true separate layer or whether they are part of the basal membrane will not be discussed in this paper. We will refer to this shortly as the ' basal layer ' or ' basal cells.' These cells proliferate rapidly in our cases of bronchiolitis. They lose their fusiform shape and grow more roundish-oblong. Within a short time (a few days are sufficient), they may produce a many-layered stratum, lining the inside of the bronchiolar tube between the elastica and the epithelium. The layer is soon vascularized by ingrowth of vessels from the adventitia, which perforate the elastica.

The epithelium undergoes various changes. Sometimes it is loosened and cast off. In most cases this is not a post-mortem effect or an artefact produced by the technique of fixation and embedding as is frequently assumed. In one case we found epithelium aspirated into the air-spaces. Sometimes the epithelium was entirely lacking; sometimes it could be seen in aggregations in the lumen: neither appearance is compatible with the detachment from post-mortem or from technical causes. A most peculiar feature is an abnormal growth of the epithelium which is frequently met with. The epithelial cells, which ordinarily in the smaller bronchioles are low and still more so in the respiratory bronchioles, assume a columnar shape of extraordinary height. The single layer which is present normally in the larger bronchioles is transformed into a kind of stratified epithelium. Between the epithelial cells more or less numerous cells can be seen migrating through to the lumen.

The lumen is more or less filled by cellular masses, monocytes and polynuclears in different proportion. The respiratory bronchioles are frequently filled by a more mucous content containing only a few cells.

The lung, as mentioned above, is as a rule not affected, or at least not at the beginning. As a consequence of the obstruction to the passage of the air, the lung tissue collapses. Since a collapsed lung is more liable to infiltration and inflammation, it is no wonder that pneumonia frequently develops. Pneumonia is not directly but only indirectly due to the bronchiolitis, the link between them being the collapse. The bronchiolar inflammation stops at the beginning of the air-spaces; the air spaces adjacent to the bronchiolar wall are not affected. Interstitial spread was not observed. Only in one case interstitial infiltration in a zone in the immediate vicinity of the bronchioli could be seen.

The lymphatic system is distinctly affected in the majority of cases. This is not peculiar, as lymphangitis occurs in numerous infections of the lung. Much more noteworthy are the widespread lymphatic nodules which were present in two cases. In one of those lymphangitis was also present. The miliary nodules are ordinarily attached to the bronchioles and less frequently to vessels. Sometimes they are at the usual place between bronchiole and pulmonary artery. The nodules often consist not only of an accumulation of lymph cells but are sometimes amply vascularized so that they resemble much

more true lymph-glands. The two cases in which the nodules were observed were older infants, of six and thirteen months.

It is well known that the type of bronchiolitis described leads frequently to bronchiolitis obliterans. This in its earliest stage was seen in the youngest infant (ten weeks). The respiratory bronchioles, and these only, were filled with mucous-like more or less homogeneous masses, which projected somewhat into the air-spaces. In these masses young vessels filled with red corpuscles and also fibroblasts could be observed. The whole duration of the illness in this case did not amount to more than twelve to fourteen days.

Discussion and conclusions

In the present cases, as mentioned above, bronchiolitis was not associated with interstitial spread, in contrast to the findings of American authors in adults. McNeil (1929) in his investigations of pneumonia in children also observed no interstitial spread, while Lauche (1928) in his comprehensive article comes to the conclusion that, in this respect, there is a difference between adults and children. The cases described in this paper are also in no way associated with alveolar pneumonia. The primary lesion is bronchiolar and is a definite anatomical and histological entity. Hitherto the purely bronchiolar nature of this condition has not been recognized. In the literature it is referred to as broncho-pneumonia. The reason for this confusion might be that the macroscopical appearance of multiple pulmonary foci and the histological picture of a patchy consolidation resembles broncho-pneumonia. These appearances are not, however, produced by peri-bronchiolar sheaths of infiltrated alveoli, but by an infiltration of the bronchiolar wall itself, which becomes greatly enlarged in consequence (fig. 1 and 2). In cases like those described by MacCallum the name ' interstitial broncho-pneumonia ' is obviously justified, because there was a widespread interstitial process originating from the inflamed bronchioli.

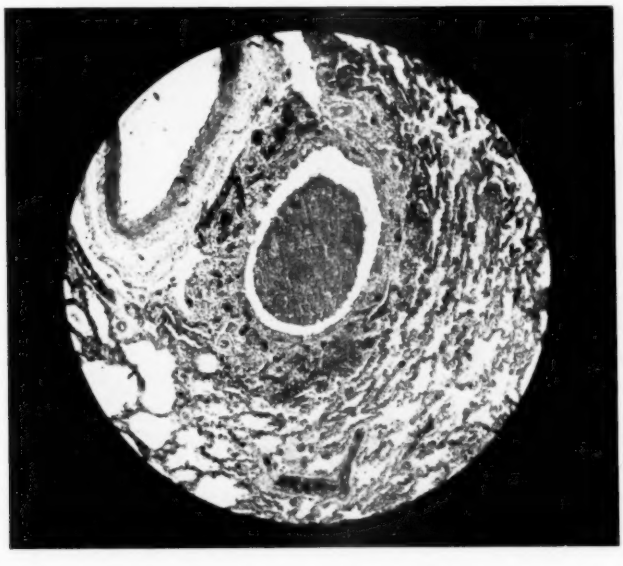


FIG. 1.—Proliferative mural bronchiolitis. Bronchiolus of 0·3 mm. diam. (× 30, Case No. 2).

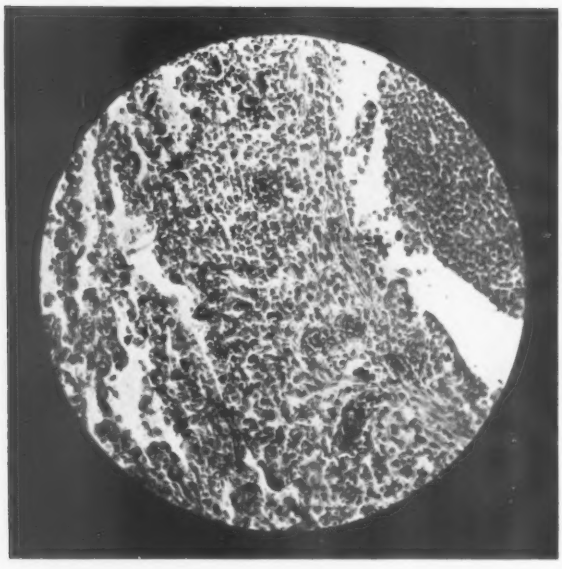
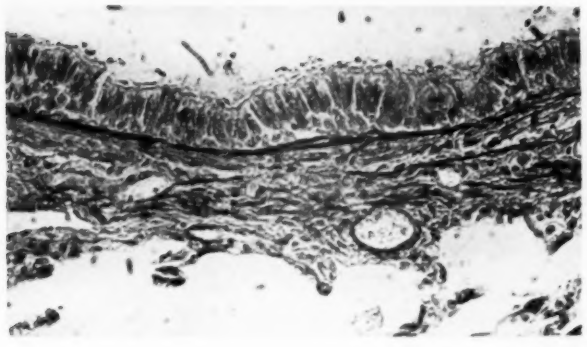


FIG. 2.—High-power view of part of fig. 1. (× 125.)

The characteristic thickening of the bronchiolar wall by hyperaemia and cellular infiltration has been described in measles and influenza many times before. McNeil and his co-workers recently referred to it. It is not necessary, therefore, to comment on its details. The proliferative changes, however, that we have described in the mucous membrane appear to be of the greatest importance. These changes are of a delicate nature and have apparently been overlooked up till now.

In order to understand these changes it seems useful to bear in mind the histological structure of the bronchiolar wall. As shown in fig. 3, 4 and 5, six components can be distinguished. Beginning from the lumen the sequence is as follows. First, columnar or cubical epithelium; second, the basal cells; third, the basal membrane; fourth, the elastic sheath; fifth, the musculature; and sixth, the adventitia. There is no tunica propria, as found in the bronchi. Of all these constituents, the basal cells, which are the least conspicuous, are the focus of interest. These cells are so small, so few and so hidden that, as a rule, they are not mentioned even by the few people who have dealt with the structure of the bronchiolar wall. Miller (1937) considers them to be analogous to the basal cells of the stratified epithelium of the trachea and the larger bronchi. Whether this is right will not be discussed in this paper.

In order to obtain a correct picture of the histological components of the bronchiolar wall it is most essential to use elastic tissue stain. In this way a clear differentiation between the mucous membrane and the rest of the bronchiolar wall is produced, as an elastic sheath forms the border between the mucous membrane and the external part of the wall. The elastica is composed mainly of fibrils running longitudinally. They are so close together that in cross sections they appear as a continuous ring when looked at with a low or a medium power. Between the elastica and the epithelium the basal cells can be observed as flat, spindle-shaped cells, scattered irregularly. They do not



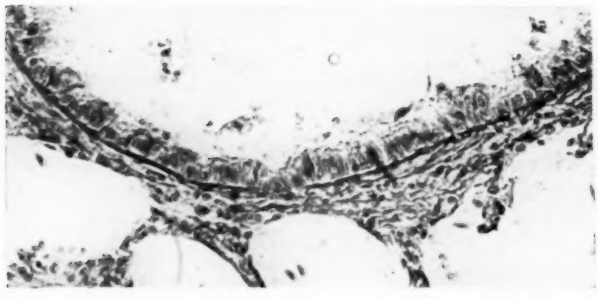


FIG. 3 and 4.—Cross section of the wall of bronchioli of 0·6 and 0·3 mm. diameter respectively. From child aged five months. (× 200, cf. diagram fig. 5.)

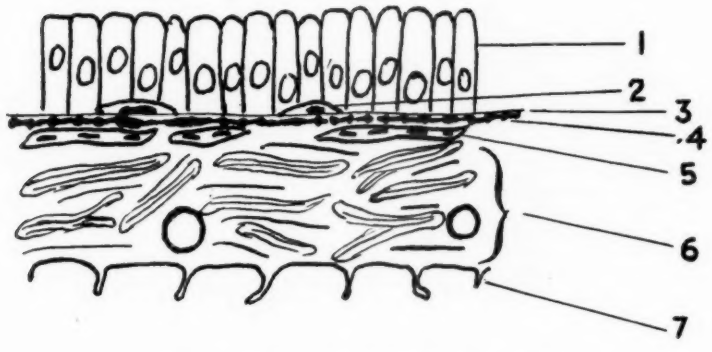


FIG. 5.—Diagram after Fig. 4, × 700.

1. Ciliated epithelium. 2. Flat basal cells. 3. Basal membrane. 4. Elastic sheath. 5. Muscles. 6. Adventitia composed of connective tissue, elastic fibres and vessels. 7. Alveolar walls.

(Bronchiolus 0·3, × 700.)

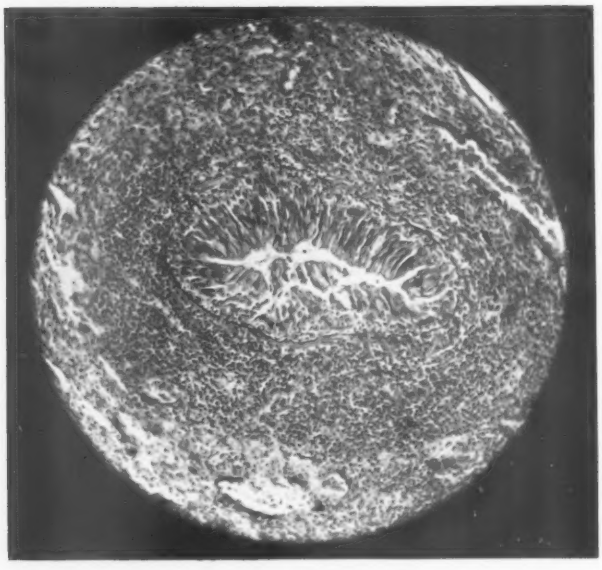


FIG. 6.—Bronchiolus of 0·3 mm. diameter, case No. 1, × 140. Infiltration of the wall. Epithelium enlarged. Between epithelium and elastica proliferated basal cells.

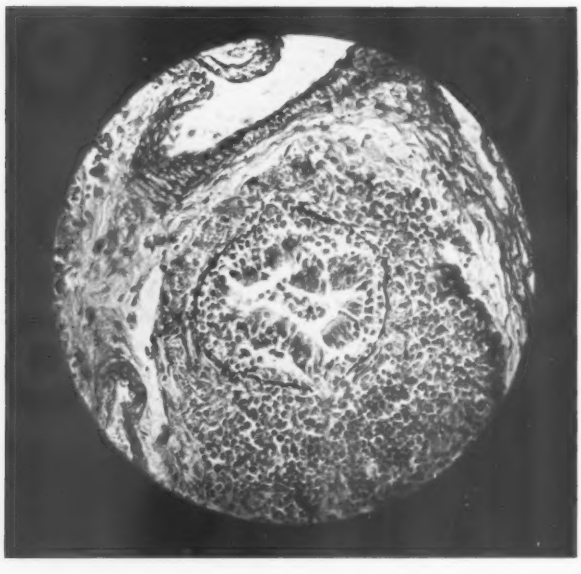


FIG. 7.—Bronchiolus terminalis, 0·18 mm. diameter, case No. 1, × 125. Infiltration of the wall, engorgement of the vessels. Lymph nodule attached to the wall. Epithelium pushed to the centre of the lumen by proliferated basal cells.

form a continuous ring. They are more likely to be seen in pathological cases such as those reproduced in the photomicrographs (fig. 6 and 7).

In our cases a surprising change in the basal cells was seen. They proliferated rapidly and formed within a few days a definite stratum between the elastica and the epithelium. The extent of the proliferation varied. Sometimes there was only a thin though quite obvious layer; sometimes it became so great that the lumen was visibly narrowed and the epithelium was pushed to the interior of the lumen (fig. 7). The enlarged basal layer can be seen in illustrations of different papers on pneumonia, bronchitis and interstitial broncho-pneumonia, but, surprisingly, no reference is made to it. Goldberger (1918) is the only one to describe the proliferation of the basal cells. This was in one case of diphtheria and he considered that it was rare and exceptional.

The proliferation occurred only in the bronchioles. Variations in the extent of the cellular growth depend on the size of the bronchioles, the age of the child and on several other factors which, however, cannot be discussed here in detail. The proliferative process does not occur where a marked basal membrane is present. Its formation depends on the age. In the newborn and the young infant only the larger bronchi are provided with a basal membrane which is visible in an ordinary histological preparation. Gradually it grows stronger within the subsequent months and, at the same time, descends to the smaller bronchi. In older children even the larger and the medium bronchioles (1·0 to 0·3 mm.) are provided with an easily discernible basal membrane.

The question why mural bronchiolitis is sometimes a proliferative one and sometimes not will be briefly discussed. In the measles-influenza type proliferation is always present. In other less specific infections proliferation is absent. Difference in the intensity of inflammation or the presence of a specific irritant might be responsible for these differences. The nature of the infecting agent seems to be the important factor, since proliferation does not occur in non-specific mural bronchiolitis even when of great intensity. Slight swelling of the basal cells which makes them more easily recognizable occurs in many cases of bronchiolitis. This cannot be confused with the abundant growth seen in our cases.

The proximity of the basal cells to the epithelium leads us to a further consideration of the epithelium. Sometimes it is merely dislodged from its base, in other cases it is completely separated. It might be found in garlands or coils somewhere in the lumen of the bronchiole. Occasionally it is surrounded by pus or mucus so that its displacement during life cannot be doubted. In still other cases no epithelium at all can be seen. If the elastic tissue is stained, it is seen that at the site of the mucosa there is nothing but a layer of proliferated basal cells.

Enlargement of the epithelium is another feature occurring in proliferative mural bronchiolitis. This is well known from the study of the lung in measles and influenza, and a great deal of discussion has taken place about its interpretation. Our contribution to this discussion is confined to one point. Is there any connexion between this hitherto unexplained growth of the epithelium

and the proliferation of the basal cells? There appear to be only two possibilities. Either the growth of the epithelium and the basal cells is stimulated by one and the same irritant or, as the proliferation of the basal cells is more constant, this layer is primarily affected. This problem will be considered in detail in a later paper.

We return now to the problem of whether the characteristic features of proliferative mural bronchiolitis might be caused by some peculiarity of the infecting agent. The histological picture presented in this paper is, as mentioned above, almost identical with that occurring in measles, whooping cough and influenza. Our cases might be of influenzal origin. This must the more be taken into consideration as several authors have found the Pfeiffer bacillus in almost every case of bronchiolitis (Opie, 1921; Liston, 1929). On the other hand, one must consider the possibility of a particular agent or of a group of agents being the cause of the same type of bronchiolitis in measles, whooping cough, influenza, etc. These agents, according to modern ideas, might belong to the virus group. Influenza and measles are now considered to be virus diseases, and some bacteriologists consider that a virus may play a part in the etiology of pertussis.

McCordock (1933) produced a typical mural bronchiolitis of the measles type by the introduction of dilute vaccine virus into the trachea of rabbits. Broncho-pneumonia could also be produced by superimposition of infection by bacteria. In a recent paper (Goodpasture et al., 1939) several cases of mural bronchiolitis in children suffering from measles and whooping cough were described as ' virus pneumonia ' because, histologically, inclusion bodies were found.

These facts, taken together, support the idea that virus infection may play an important part in P.M.B.

We will conclude by saying there is no clear-cut clinical picture corresponding to the definite anatomico-histological appearance. The general clinical symptoms were those of an ordinary broncho-pneumonia. There was considerable respiratory distress, with dyspnoea and cyanosis. This is not to be wondered at when one examines the anatomical lesion. The obstruction of so many bronchioles and the consequent collapse of the air-spaces diminish the respiratory surface very considerably.

In cases of acute respiratory infections in infants, causing considerable respiratory embarrassment, the physician should bear in mind the possibility of bronchiolitis and not make a general diagnosis of broncho-pneumonia in all such cases.

Summary

1. Bronchiolitis can be classified into ' catarrhal ' and ' mural ' types. The latter must be subdivided into ' simple,' ' proliferative ' and ' destructive ' bronchiolitis.

2. Proliferative mural bronchiolitis is the type occurring in measles and influenza. We observed this type in several infants who did not apparently suffer from either of these infections.

3. The gross change is an enormous thickening of the bronchiolar wall and collapse of the lung tissue.

4. This, and not peribronchiolar infiltration, is responsible for the macroscopical picture of ' disseminated broncho-pneumonia.'

5. The centre of the lesion is situated in the medium bronchioles. Larger bronchioles, especially when furnished with a definite basal membrane, and bronchi are much less affected. This applies to the infiltration of the wall as well as to the engorgement of the vessels.

6. The proliferative part of the lesion affects predominantly the basal cells and the epithelium.

7. True pneumonia may develop as a consequence of mural bronchiolitis, but this is a secondary process.

8. Many facts point to the possibility of virus infection as a cause of proliferative mural bronchiolitis.

9. The clinical picture in our cases was indefinite. The possibility that proliferative mural bronchiolitis might be a disease sui generis is put forward for discussion.

Thanks are due to the honorary staff of The Hospital for Sick Children for the opportunity to carry out this investigation and for permission to use the post-mortem and case records.

References

Engel, St. (1935). *Handbook of Children's Diseases*, **3,** ed. by Pfaundler and Schlossmann, London.
Feyrter, F. (1925). *Virchows Arch.*, **255,** 753.
Goldberger, F. (1918). *Zbl. allg. Path. path. Anat.*, **29,** 510.
Goodpasture, E. W., et al. (1939). *Amer. J. Dis. Child.*, **57,** 447.
Hart, C. (1904). *Dtsch. Arch. klin. Med.*, **79,** 108.
Huebschmann, P. (1917). *Beitr. path. Anat.*, **63,** 202.
Jochmann, G., and Moltrecht (1904). *Ibid.*, **51,** 251.
Laidlaw, P. P. (1935). *Lancet*, **1,** 1118.
Lange, W. (1901). *Dtsch. Arch. klin. Med.*, **70,** 342.
Lauche, A. (1928). *Handbuch Path. Anat.*, vol. 3, part I, 701.
Liston, W. G. (1929). *Arch. Dis. Childh.*, **4,** 283.
MacCallum, W. G. (1919). *The Pathology of the Pneumonia in the United States Army Camps*, New York.
McNeil, C. (1929). *Arch. Dis. Childh.*, **4,** 83, 111.
McCordock, H. A., and Muckenfuss, R. S. (1933). *Amer. J. Path.*, **9,** 221.
Miller, W. S. (1937). *The Lung*, Springfield.
Moncrieff, A. A. (1934). *Diseases of Children*, Ed. by Thursfield and Paterson, London, p. 424.
Opie, E. L., et al. (1921). *Epidemic Respiratory Disease*, St. Louis.
Policard, A. (1938). *Le Poumon*, Paris.
Straub, M. (1937). *J. Path. Bact.*, **45,** 75.

GAUCHER'S DISEASE

DIAGNOSIS BY STERNAL PUNCTURE AND IMPROVEMENT FOLLOWING SPLENECTOMY

BY

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The disturbance of lipoid metabolism, known as Gaucher's disease, is a relatively rare condition, although in the past twenty years there has been an increase in the number of reports of the disease, due to its more frequent recognition.

First described in France by Ernest Gaucher in 1882, the second report was made in England by Collier in 1895. Subsequent accounts mostly came from the Continent and America, and by 1926 Pick was able to collect thirty-nine authenticated cases from the literature, of which five were seen and reported by him personally. In 1929 Hoffmann and Makler collected and analysed eighty-nine reports. Since then case reports have gradually increased in number, and the total must now be nearing two hundred. The number of cases recorded from Britain form a comparatively small percentage of these.

The disease, apparently congenital, is due to an upset of lipoid metabolism, in which cerebroside (kerasin) is found in the typical Gaucher cells of the affected tissues and organs. The occurrence of the disease in several members of the same family has frequently been observed, and although there is slight evidence that it may be hereditary (Anderson, 1933; Bloem, Groen and Postma, 1936), such cases are exceptional.

It is noteworthy that many of the cases have occurred in Jews, although this is by no means a constant finding. Packman (1938) recorded the disease in a brother and sister who were negroes, and Aballi and Kato (1938) reported two cases in a Japanese family. Females are more often affected than males, and symptoms usually appear during the first decade of life, although several cases have been reported in which the symptoms did not appear till middle age (Bloem, Groen and Postma, 1936). The infantile type of the disease is acute and less typical (Oberling and Woringer, 1927; Moncrieff, 1930; Rowland, 1936; Aballi and Kato, 1938).

Case report

A Jewish boy, aged ten years, was brought by his parents to the Royal Infirmary, Manchester, on October 2, 1939. He complained of swelling of the abdomen, weakness and loss of flesh. His parents stated that they had noticed

that the child's abdomen had been swollen since infancy, and as time had gone on this had become more pronounced.

Up to the age of nine the boy had felt perfectly fit and had had no complaints. He was energetic, and was in the ' scholarship class ' at school. In the spring of 1938 he became listless and easily tired, but after his summer holidays he seemed to improve. In the following November he complained of pain in the left side of the chest and abdomen, and was admitted to a hospital, where he remained for two weeks under observation.

The pain having disappeared he was discharged, but was re-admitted to the same hospital two days later on account of epistaxis. On this occasion he was treated with a prolonged course of oral iron and parenteral liver extract for splenomegaly associated with anaemia and leucopenia. During this time epistaxis, although not severe, had occurred on several occasions, and he had also suffered from subconjunctival haemorrhages. His abdomen had become more swollen and he had lost further weight. No pigmentation of the skin had been noticed. He was discharged in July, 1939, and during the three months he had been at home his condition had got progressively worse. There had been no further haemorrhages, however. By September, 1939, the boy could only walk a short distance on account of the dragging weight of his abdomen.

Previous health. At the age of eighteen months he had suffered from enlarged cervical glands, but these had subsided in a few weeks. He had also suffered from mild attacks of whooping cough, measles, ? scarlatina and chickenpox. Since the age of nine years he had worn glasses on account of myopia.

Family history. His sister, aged six years, had always been perfectly healthy, as were his parents. Their clinical findings and blood counts were normal. There was no known history of blood disease, jaundice or abdominal swelling in his forebears on either side of the family.

Clinical examination. Clothed, the boy looked pale and ill. He had a pronounced malar flush. The abdomen was very prominent, and he walked with his shoulders thrown back so as to counteract the drag of the swelling. Stripped, he looked a pathetic sight, there being gross abdominal swelling associated with wasting of the thorax and limbs (fig. 1). The greatest circumference of the abdomen was two inches above the umbilicus where it measured twenty-eight inches. His weight was 3 stone 12 lb., and he was 4 feet 1 inch in height. There was visible pulsation in the vessels of the neck, and a few small dilated veins were noted in the epigastrium and around the umbilicus, which was everted.

There was pronounced pallor of the skin and mucous membranes, and small discrete movable glands were palpated in both sides of the neck, and in the groins and axillae. There was no jaundice, cyanosis or oedema, and no evidence of pigmentation of the skin, apart from a melanotic naevus below and to the right of the umbilicus. The sclerae were of a bluish tinge but no pingueculae were present. Both tonsils were considerably enlarged.

An enormous spleen could be felt filling practically the whole abdomen. The margin of the hand could just be put between the lower edge of the spleen and pubes. A splenic notch was easily felt. There was no abdominal tenderness. The liver was just palpable below the right costal margin. There were no signs of ascites. The lungs were apparently clear; at the left base the percussion note was impaired due to the enlarged spleen. Pulse rate varied from 80 to 90 per minute, and the heart sounds were soft, there being frequent extrasystoles. Blood pressure 115/70 mm. Hg.

No abnormalities were noted on examination of the genito-urinary and nervous systems. Apart from general pallor of the fundi no abnormality was found on ophthalmoscopic examination.

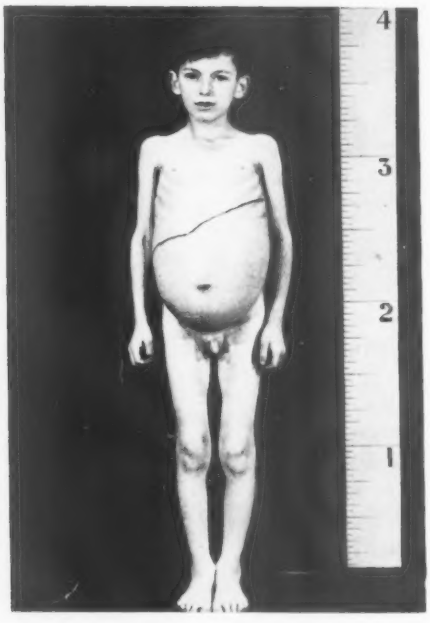

FIG. 1.—Appearance of boy suffering from Gaucher's disease three weeks before splenectomy. Upper border of the spleen is outlined in black.

Special investigations. Blood counts showed a hypochromic anaemia, associated with leucopenia and thrombocytopenia (table 1). The mean cell volume of the erythrocytes was 83 microns. Haemolysis of the red cells began at 0·46 per cent. saline and was complete at 0·32 per cent. saline. The direct van den Bergh reaction was negative, and the serum contained 0·8 units bilirubin.

Bleeding time was 2 min. 3 sec. (normal for method 2 to 5 min.), coagulation time 2 min. 40 sec. (normal for method 1½ to 3 min.). Examination of material obtained by sternal puncture showed a hyperactive cellular marrow with an increase of erythroblasts and normoblasts. Leucopoietic elements appeared reduced in number. In addition Gaucher cells, with typical reticulated cytoplasm and eccentric nuclei were seen. These characteristic large cells, however, were comparatively few in number.

Other investigations:

Blood cholesterol ..	130 mgm. per cent.
Blood lipoid phosphorus ..	13·2 mgm. per cent.
Blood fat	1·08 grammes per cent. (fasting).
Serum calcium	10·6 mgm. per cent.
Blood phosphatase	3·6 units (Bodansky's method).
Blood urea	24 mgm. per cent.

The urine was normal as judged by routine tests. The Wassermann reaction gave an unsatisfactory result on two occasions, fixation of complement occurring in the absence of antigen. The Kahn and Meinicke tests were both negative.

Glucose and laevulose tolerance tests were within normal limits, and x-rays of the skeleton showed no changes in the bones, apart from a slight trabeculation in the middle thirds of both tibiae which, in the opinion of the radiologist, was probably not of pathological significance.

Subsequent progress. As his parents were unwilling that the boy should come into hospital, he was brought regularly by them to the out-patient clinics,

TABLE 1

DATE	2.10.39	9.10.39	2.11.39	TRANSFUSIONS AND SPLENECTOMY	8.11.39	23.11.39	8.2.40	11.4.40	13.6.40	20.7.40
Erythrocytes, per c.mm.	3,470,000	3,190,000	2,910,000		5,050,000	4,540,000	4,820,000	4,766,000	4,940,000	4,900,000
Leucocytes, per c.mm.	3,600	1,800	3,000		5,800	16,000	24,400	26,800	12,800	19,600
Haemoglobin, per cent. (Haldane) ..	62	54	46		74	80	89	90	93	92
Colour index	0·89	0·85	0·81		0·74	0·88	0·92	0·94	0·94	0·94
Neutrophil polymorphs, per cent. .	64·5	52·5	54·0		54·0	61·0	44·0	82·0	47·0	52·0
Lymphocytes, per cent.	30·5	41·5	41·0		38·0	28·0	40·0	17·0	40·5	38·5
Monocytes, per cent.	4·0	6·0	4·0		5·0	2·5	4·5	1·0	6·5	6·0
Myelocytes, per cent.	Nil	Nil	1·0		2·0	Nil	Nil	Nil	Nil	Nil
Eosinophils, per cent.	1·0	Nil	Nil		1·0	8·5	11·5	Nil	5·5	3·5
Basophils, per cent.	Nil	Nil	Nil		Nil	Nil	Nil	Nil	Nil	Nil
Platelets, per c.mm.	38,800	39,600	45,000		269,000	400,000	386,000	392,000	442,000	408,000
Reticulocytes, per cent.	9·6	—	—		—	1·1	0·8	—	—	1·1
Anisocytosis and poikilocytosis ..	Marked	Marked	Marked		Marked	Slight	—	—	—	—

A few nucleated red cells were noted in the peripheral blood during the week following the operation.

where he was treated with oral iron. By the end of three weeks, however, his general condition was deteriorating so rapidly that he had to be admitted. By this time the sternal puncture result had clinched the diagnosis of Gaucher's disease (fig. 2), and although operation risk seemed great the opinion of a surgeon was sought with a view to performing splenectomy. The patient's condition became even worse and he had another epistaxis on October 30, 1939. His temperature had been intermittently raised.

The boy's parents consented to the operation in spite of the obvious risk involved, and on November 8, 1939, after a pre-operative drip transfusion of

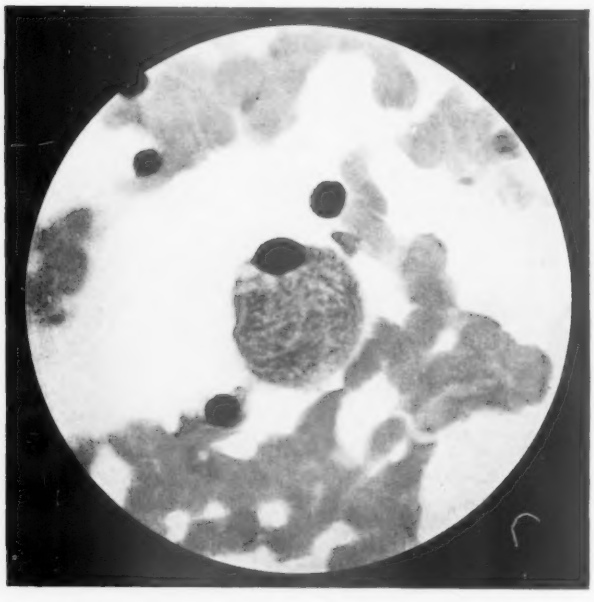

FIG. 2.—Gaucher cell in bone marrow obtained by sternal puncture. (Jenner-Giemsa × 750.)

FIG. 3.—Appearance nine weeks after splenectomy.

600 c.c. citrated blood, splenectomy was successfully carried out by Mr. H. H. Rayner.

The spleen was delivered through a right paramedian incision six inches in length. Dense adhesions were found between the upper pole of the spleen and the diaphragm and, on attempting to break these a necrotic area ruptured with the escape of grumous material, yellow in colour and odourless. The liver, which was enlarged about one-and-a-half inches below the right costal margin, was noted as being pale with fine yellowish mottling.

After the operation another drip transfusion, of 450 c.c. blood and 200 c.c. saline was given. The patient made satisfactory progress subsequently and five weeks later he was up and walking about. He felt very well and was putting on weight and improving in colour. Glands were still palpable in the neck, groins and axillae as before, although probably due to his improved nutrition they were not so easily detected (fig. 3).

The blood count figures rose dramatically after the transfusion and splenectomy (table 1), and this improvement was maintained without further treatment.

At the end of two months his weight was 4 stone 3 lb. Sternal puncture, at this time, showed the erythropoietic hyperplasia to have diminished, and the proportion of leucopoietic elements to have increased. Gaucher cells were

present in about the same numbers as before. Reticulocytes in the peripheral blood had fallen to normal. X-rays of the skeleton showed no pathological change.

At the beginning of April, 1940, he reported complaining of a sore throat and swollen cervical glands. His tonsils were greatly enlarged. Removal of tonsils and adenoids was performed by Mr. F. G. Wrigley on April 10, 1940. His general health has continued to improve up to the time of writing (nine months after the operation). Recently (July, 1940) his weight was 5 stone and sternal puncture showed Gaucher cells to be present in approximately the same numbers as before the operation. There was, however, no radiological evidence of disease throughout the skeleton.

Morbid anatomy of the spleen, tonsils and adenoids

The weight of the spleen removed at operation was 3,530 grammes. It was firm and of a dark purple colour with yellow mottling. The surface showed numerous infarcts of varying size and the capsule was thickened. There was a large ruptured necrotic area at the upper pole where it had been adherent to the diaphragm (fig. 4). On section the spleen was dense in consistency and of a

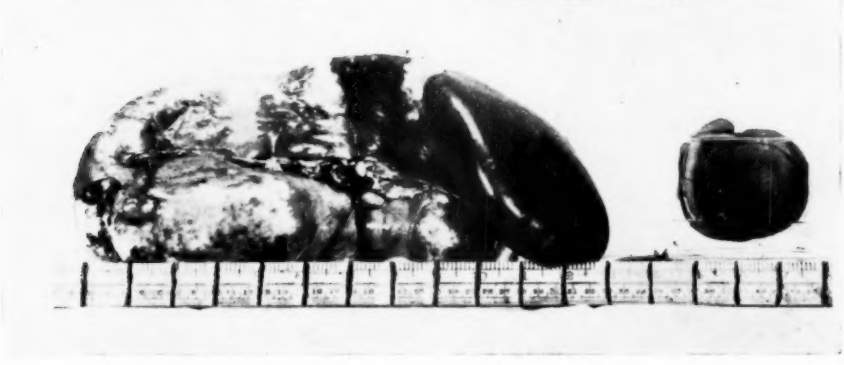

FIG. 4.—Spleen removed at operation compared with normal adult spleen. Scale in inches.

deep red colour. Numerous small greyish-white spots were noted on the cut surface. Histological examination showed the spleen to be packed with Gaucher cells and the lymphoid follicles were widely separated from one another. The large characteristic Gaucher cells varied in shape and size, but were mostly spherical or ovoid. The great majority of them had a relatively small single nucleus, often eccentrically placed within the cell but some were multinuclear. The cytoplasm of the cells was pale and reticulated and some showed vacuoles. These appearances were well seen in sections stained with Mallory's stain and Masson III in paraffin sections of both formalin and Helly fixed material (fig. 5). Frozen sections, stained by Sudan III, did not show any fat staining. The Schultze reaction for cholesterol was negative. Frozen sections of formalin fixed spleen and also fresh dry smears from bone marrow did not show any doubly-refractile bodies in the Gaucher cells under ordinary conditions, but when mounted in pure glycerin and employing a strong illuminant feebly anisotropic bodies suggesting the form of vesicular crystals were seen in the cells. These apparently crystalline forms corresponded very well to the spaces present in the reticulated cytoplasm of the cells. This appearance, possibly due to the refractive index of the mounting medium, was present at room temperature and was not increased to any appreciable extent by heating and cooling the frozen sections of the spleen. Heating in water was not found

to cause doubly-refractile bodies to appear in the cells (cf. Graham and Blacklock, 1927).

Histological examination of the tonsils and adenoids, removed at operation, showed signs of chronic inflammation but no Gaucher cells were found.

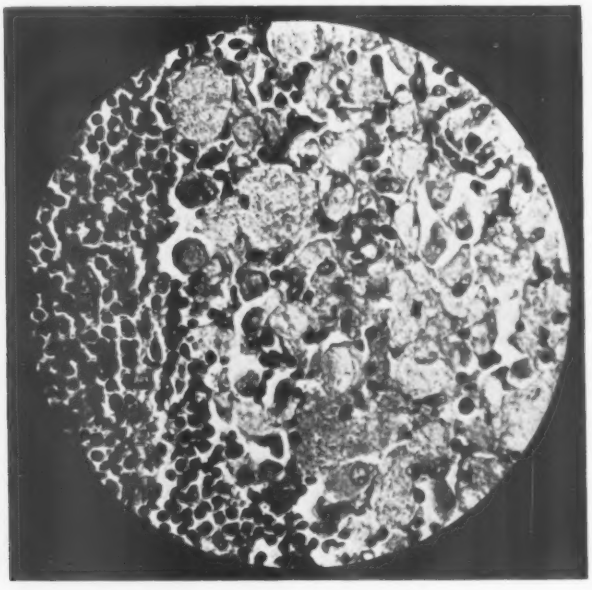

FIG. 5.—Gaucher cells in spleen. (Masson III × 300.)

Chemical analysis of the spleen

(In collaboration with Dr. F. X. Aylward)

Six hundred and twenty grammes of the spleen were minced and extracted with three litres of cold alcohol and three litres of ether. The alcohol-ether extract contained most of the glyceride cholesterol and phosphatides of the spleen. The residue was extracted exhaustively with chloroform at 60° C. and filtered through a hot funnel. The hot chloroform extract contained mainly cerebrosides and sphingomyelin. The extract was taken to dryness and weighed. 20·9 grammes were obtained, or approximately 4 per cent. of the wet weight of the spleen.

The solid obtained agreed with the known properties of cerebrosides, being insoluble in cold alcohol and ether, and being soluble in hot alcohol or hot chloroform. On cooling these hot concentrated solutions a white precipitate readily appeared, in the form of a gel.

On crystallizing out from a dilute hot alcoholic solution, a white solid resulted which macroscopically appeared to have a definite crystalline form. Under the microscope crystalline needles which formed star-shaped aggregations, somewhat similar to crystals of kerasin illustrated by Pick (1933) were seen (fig. 6). The form of the crystals varied in arrangement but were mostly star shaped. Under the polarizing microscope they were strongly doubly-refractile.

Of the crude material obtained 3·3 grammes were dissolved in hot alcohol, precipitated with saturated solution of $HgCl_2$ and the precipitate separated off by centrifuging. The precipitate was dissolved in hot alcohol and Hg was removed by means of H_2S. The filtered solution was then taken to dryness and recrystallized from alcohol yielding 0·86 grammes of a white solid.

The physical properties of the purified material were similar to those of the crude dry extract. Similar doubly-refractile crystals were obtained. Analysis showed that phosphorus was absent, thus excluding sphingomyelin. Micro-

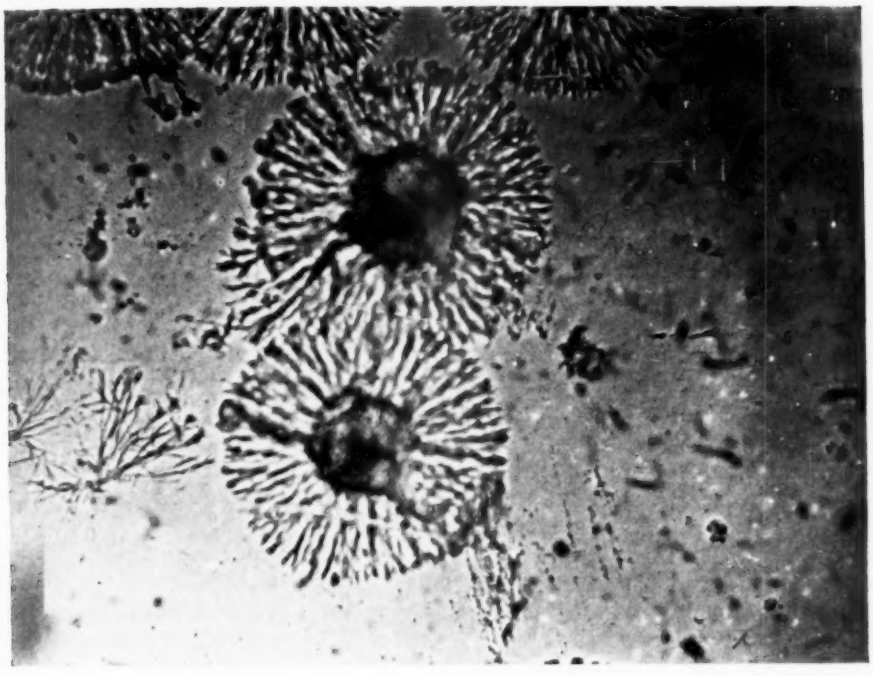

FIG. 6.—Crystalline aggregations of kerasin obtained from Gaucher spleen (×400).

analysis of the purified material (Weiler and Strauss, Oxford) gave the following percentages :

C	H	N
70·26	11·21	2·2

The results reported compare favourably with the findings of several other workers (table 2), although the nitrogen figure is somewhat higher.

TABLE 2

ELEMENTARY ANALYSES OF PURIFIED CEREBROSIDE DERIVED FROM GAUCHER SPLEENS

	C PER CENT.	H PER CENT.	N PER CENT.
LIEB (1927)	69·76	11·24	—
LIEB AND MLADENONIC (1929)	70·74	11·35	1·98
MCCONNELL, FORBES AND APPERLEY (1939)	70·60	11·23	1·73
PRESENT CASE	70·26	11·21	2·20

Examination of the crystals (Dr. H. E. Buckley) employing the selenite plate test as described by Rosenheim (1914) showed that the appearances were consistent with the substance being pure kerasin. No phrenosin was present as judged by this test.

Gaucher's disease: etiology and pathology

Gaucher originally described the condition as a primary epithelioma of the spleen, whereas Bovaird (1900) considered it to be an endothelial hyperplasia of the spleen, liver and lymph nodes. Brill, Mandlebaum and Libman (1905) first discovered the typical cells in the bone marrow, and in 1907 Schlagenhaufer designated the condition an affection of reticulum cells of all the lymphatic and haemopoietic organs. In the same year Marchand emphasized the importance of the foreign substance in the cells.

Mandlebaum and Downey (1916) founded the modern conception of the disease as a metabolic disturbance, and Lieb (1924) and Epstein (1924) showed that the cerebroside, kerasin, was the abnormal substance stored. It is now recognized that reticulum cells are almost exclusively affected by the disease, but the exact nature of the process is unknown. Whether 'storage' corresponds to an increased ingestion or diminished excretion by the cells involved, remains an open question. Pick (1933) favours the view that increased intake by the cells is the most likely explanation, although Jaffé (1938) quotes Tropp as holding the view that the piling up of kerasin in affected cells is due to a defect of mobilization and transport, or an increased production by the cells, and Tannhauser (1933) suggests that kerasin is produced at the expense of either the sphingomyelin or sphingosine present in the body.

Certain workers (Lieb and Mladenonic, 1929; Capper, Epstein and Schless, 1934) have reported the presence of small amounts of phrenosin as well as kerasin in Gaucher spleens, but the amount is small and is not constantly found (McConnell, Forbes and Apperly, 1939). The cholesterol content of the spleen is not increased (Cushing and Stout, 1926; Thomson and Wright, 1937).

According to Rosenheim (1916) the formula for kerasin is $C_{47}H_{91}O_8N + H_2O$, and analyses have shown that kerasin may form up to 10 per cent. or more of the dry weight of the spleen. Cushing and Stout (1926) found crude cerebroside to form 16 per cent. of its dry weight. Chemical studies of the blood have failed to show any definite changes.

The morbid anatomy of the disease gives a clear-cut picture, although the degree of involvement of various organs varies considerably. The spleen may weigh over 8,000 grammes (Brill, Mandlebaum and Libman, 1909), and although the liver enlargement is relatively less it is frequently twice its normal weight (Pick, 1933). Bone marrow and lymphatic glands (more frequently intra-abdominal and intra-thoracic) are also affected, and rarely the lungs (Merklen, Waitz and Warter, 1933; Myers, 1937) and kidney (Horsley, Baker and Apperly, 1935) may contain Gaucher cells. Although it is likely that Gaucher cells may be present in the brain and meninges (Myers, 1939) definite evidence of this appears to be lacking.

The characteristic Gaucher cells found in affected organs and tissues are of large size (20 to 80 μ in greatest diameter) with pale reticulated cytoplasm in which vacuoles may be seen. The nucleus is relatively small and eccentrically placed and multinuclear cells may be found occasionally. They are ovoid or polyhedral in shape, although those present in bone marrow are frequently elongated, with an irregular cytoplasmic outline.

In the spleen and liver haemosiderin deposits occur in endothelial cells, but the Gaucher cells themselves contain hardly any pigment. Those in lymphatic

glands contain haemosiderin in greater quantity (Pick, 1933). The cells do not react with stains for fatty substances, and are not doubly refractile. Graham and Blacklock (1927) made the observation that if frozen sections of fresh spleen were heated in water or glycerin to 100° C. the cells took on Sudan III stain to a slight extent and became doubly refractile. They attributed this phenomenon to hydrolysis or the running together of lipoids present in the diffuse phase. Although the lipoid substance is not doubly refractile in fresh tissues under ordinary conditions, it appears anisotropic after chemical extraction and crystallization, as was shown in the present case.

The disease is associated with a hypochromic anaemia, although in some cases this may be slight (Bonta, 1930). Leucopenia, frequently with relative lymphocytosis, is almost constantly present. The finding of a 'rather marked leucocytosis' (Enzer, 1933) must be regarded as exceptional. Thrombocytopenia is also a feature of the disease. Hyperfunction of the spleen and involvement of the bone marrow by Gaucher cells have both a part in causing anaemia.

Clinical findings and the course of the disease

In the infantile type of the disease, the clinical picture is usually one of acute involvement of the nervous system, there being paralysis, nuchal rigidity and opisthotonus associated with cachexia and enlargement of the spleen and liver. These cases are rapidly fatal.

The chronic form of the disease may be present for several decades before giving rise to symptoms, although the condition is usually recognized in childhood. The splenic enlargement may be detected in routine examination, or medical advice may be sought on account of abdominal distension, discoloration of the skin or haemorrhages.

An ochre pigmentation of the skin, more especially of the exposed parts, has been found in approximately half the cases reported. Bloem, Groen and Postma (1936) noted a patchy pigmentation of the legs, which had a sharply defined lower margin, just below the ankles. About 15 per cent. of the cases exhibit wedge-shaped thickenings of the sclerae (Hoffmann and Makler, 1929). Pick (1933) regards both these phenomena as evidence of haemochromatosis which becomes more pronounced during the course of the disease. Malar flush and myopia have been noted in several cases by Bloem, Groen and Postma (1936).

The spleen is greatly enlarged and may extend into the pelvis. Enlargement of the liver is also present but is relatively less than that of the spleen. Only occasionally are superficial lymphatic glands involved. Pains in the lower ends of the femora, tibiae, sternum or spine indicate skeletal involvement by the disease process, and swellings near the joints may be present. On occasion bone involvement has been so pronounced as to warrant the term 'osseous form of Gaucher's disease' (Pick, 1926; Melamed and Chester, 1938).

The course of the disease is slowly progressive and some cases live to over fifty years of age. Even with the enormous enlargement of the spleen and liver

symptoms may be extraordinarily slight. Death takes place from intercurrent disease, leucopenia favouring infection. In the terminal stages cachexia may be pronounced.

Diagnosis

In the differential diagnosis of the disease the following conditions must be excluded: leukaemia, haemolytic anaemia, 'splenic anaemia,' congenital syphilis, tuberculosis, rickets, Niemann-Pick's disease, Tay Sachs' disease and parasitic infections such as malaria. Some cases of the osseous type of the disease have been primarily regarded as osteomyelitis (Capper, Epstein and Schless, 1934; Myers, 1937). The infantile type may simulate intracranial disease such as meningitis.

Blood examination and probability help to rule out many of the above possibilities. There are no pathognomonic signs or symptoms, but the finding of leucopenia and thrombocytopenia associated with gross splenomegaly and liver enlargement should always bring to the mind the possibility of Gaucher's disease; if in association with skin pigmentation and thickenings of the sclerae the diagnosis is even more likely. X-rays may show destructive changes and rarefaction of the bones, and flask-like expansions of the lower ends of the femora (Junghagen, 1926; Reiss and Kato, 1932; Welt et al., 1929; Worth, 1936).

Only by biopsy can an absolute diagnosis be made. The method most frequently described is that of splenic puncture. Originally described by Bernstein (1915) it has been reported as a reliable method devoid of danger (Graham and Blacklock, 1927). Excision of a lymph gland has also been described as a method of making a pathological diagnosis (Hoffmann and Makler, 1929). There are now several cases on record in which examination of the bone marrow has effected an absolute diagnosis. Among these may be quoted the reports by Welt et al. (1929), Sokolowsky (1932), Fleischhaker and Kilma (1936), Aballi and Kato (1938) and Schartum-Hansen (1938). However, a case described by Schleussner and Schnee (1939) showed no Gaucher cells on sternal puncture, but splenic puncture established the diagnosis. Thus, although it cannot be claimed that the absence of the typical cells excludes the possibility of Gaucher's disease, a positive result dispenses with the procedure of splenic puncture, a proceeding to be avoided if possible in a patient with a haemorrhagic diathesis.

Treatment

Medical treatment of the disease is unsatisfactory; Potter and Macrae (1933) noted some clinical improvement following injections of liver extract, but other patients, including the one described here, have failed to show any benefit from this form of treatment. Radiotherapy may cause some diminution in size of the spleen, but has no effect on the course of the disease (Pick, 1933).

With regard to splenectomy, opinions are divided. Some authorities state that the operation is contraindicated, whilst others claim successful results following removal of the spleen. Pick (1933) states that the operation is

associated with a mortality of about 20 per cent. and that in most cases removal of the spleen causes skeletal involvement to become more pronounced. He admits, however, that a number of cases show improvement in general nutrition and condition of the blood after the operation, and that from a symptomatic standpoint splenectomy has a definite value.

Reviewing the literature there is now a fair proportion of cases where the operation has resulted in marked general improvement, and although no claim can be made of a 'cure' the patients may remain in a satisfactory clinical condition for many years.

Hunter and Evans (1929) recorded a case of a woman aged sixty, who was well thirteen years after splenectomy. They stated that the operation caused complete relief of symptoms. The Mayos (1935) reported a series of nine cases treated by splenectomy, in which there were two hospital deaths and two deaths subsequently. Five of the patients were alive, one of them having had four children during the eleven years following the operation.

Ogilvie (1937) operated on two sisters suffering from Gaucher's disease; one of them who had marked skeletal involvement died six hours after splenectomy, but the other was well two years afterwards, with a normal blood picture.

Among others who found splenectomy to be followed by general improvement may be mentioned Mandlebaum (1919), Bloom (1925), Graham and Blacklock (1927), Bonta (1930), Capper, Epstein and Schless (1934), Lowinger (1935), Bessie (1937), Pack and Silverstone (1938) and Webster (1938).

The size of the spleen is no contraindication to the operation; Ogilvie (1937) successfully removed one weighing 13½ lb. Although the procedure is admittedly associated with risk, it is justifiable from the standpoint that all other forms of treatment are useless. It is hardly worth while considering the operation when skeletal involvement is present to any appreciable extent. Haemorrhagic diathesis does not necessarily exclude the performance of splenectomy, but in such cases pre-operative transfusions are required.

It is not possible to state how long a patient may remain well after the operation, but the resulting improvement may be maintained for many years, although this is by no means always the case. Detailed reports of cases followed up after operation are not numerous, but it would seem that some cases may remain well for fifteen years or more after splenectomy. Naturally the degree of involvement of other organs besides the spleen at the time of operation bears a direct relationship to the prognosis. In an appreciable number of cases splenectomy seems to have checked the progress of the disease to some extent. The ultimate prognosis, however, is always bad.

Comment

The history and clinical and haematological findings in the case described strongly suggested a diagnosis of Gaucher's disease. The superficial lymphadenopathy was of interest as very few of the recorded cases have shown this.

The absence of skin pigmentation, thickenings of the sclerae and x-ray evidence of skeletal involvement, in spite of the apparent advanced stage of the

disease, were also noteworthy. The anaemia did not respond to iron or liver extract.

The pathological diagnosis, made by sternal puncture, obviated the employment of splenic puncture, which was considered hazardous on account of the low platelet count and poor general condition of the child.

It is suggested that sternal puncture which causes the patient little or no inconvenience should always be performed before splenic puncture in a suspected case. The former has the additional value of giving information concerning the haemopoietic activity of the marrow, and can exclude such conditions as atypical leukaemias.

The spleen (3,530 grammes) formed slightly over an eighth of the body weight of the patient. His immediate post-operative improvement was striking. The platelet count rose to 680,000 per c.mm. then gradually fell to within the normal range. Without further treatment eight months after splenectomy, the anaemia had improved, the red cell count and haemoglobin values being normal. The leucocyte count, which rose abruptly following the operation, remained at a level above the normal limits, and a proportional increase of eosinophils was frequently observed.

Although sternal puncture performed during the eight months following the operation showed Gaucher cells present in about the same numbers as before no radiological evidence of osseous disease was noted.

The boy's general condition has continued to improve dramatically since the operation. Examination of his tonsils and adenoids, which were removed on account of chronic enlargement, failed to show any Gaucher cells. Chemical investigations carried out on the spleen gave results comparable with those of other workers. A lipoid fraction obtained, which was insoluble in ether and soluble in hot alcohol, was identified as cerebroside.

Summary

(1) A case of Gaucher's disease occurring in a nine-year-old Jewish boy is described.

(2) Diagnosis was effected by sternal puncture.

(3) There was great clinical improvement following splenectomy.

(4) Chemical analysis showed that crude cerebroside formed approximately 4 per cent. of the wet weight of the spleen. This material, when purified, was shown to have the physical and chemical characteristics of kerasin.

Thanks are due to Dr. J. F. Wilkinson for facilities given for the study of this case, to Mr. H. H. Rayner for performing splenectomy and to Prof. S. L. Baker and Sir Robert Muir for valuable advice. Much helpful assistance was given by the technical staff of the Research Department and Clinical Laboratory of the Manchester Royal Infirmary. The photomicrographs of bone marrow and spleen were kindly taken by Mr. John Kirkpatrick.

References

Aballi, A. J., and Kato, K. (1938). *J. Pediat.*, **13**, 364.
Anderson, J. P. (1933). *J. Amer. med. Ass.*, **101**, 979.
Bernstein, E. P. (1915). *Ibid.*, **64**, 1907.

Bessie, E. M. (1937). *Med. Rec.*, **145,** 403.
Bloem, T. F., Groen, J., and Postma, C. (1936). *Quart. J. Med.*, **5,** 517.
Bloom, W. (1925). *Amer. J. Path.*, **1,** 595.
Bonta, M. B. (1930). *Arch. Surg., Chicago*, **21,** 851.
Bovaird, D. (1900). *Amer. J. med. Sci.*, **120,** 377.
Brill, N. E., Mandlebaum, F.S., and Libman, E. (1905). *Ibid.*, **129,** 491.
——, ——, —— (1909). *Ibid.*, **137,** 849.
Capper, A., Epstein, H., and Schless, R. A. (1934). *Ibid.*, **188,** 84.
Collier, W. (1895). *Trans. path. Soc. Lond.*, **46,** 148.
Cushing, E. M., and Stout, A. P. (1926). *Arch. Surg., Chicago*, **12,** 539.
Enzer, N. (1933). *J. Amer. med. Ass.*, **101,** 981.
Epstein, E. (1924). *Biochem. Z.*, **145,** 398.
Fleischhaker, H., and Kilma, R. (1936). *Münch. med. Wschr.*, **83,** 2051.
Gaucher, E. (1882). *De l'épithélioma primitif de la rate*, Thèse de Paris.
Graham, S., and Blacklock, J. W. S. (1927). *Arch. Dis. Childh.*, **2,** 267.
Hoffmann, S. J., and Makler, M. I. (1929). *Amer. J. Dis. Child.*, **38,** 775.
Horsley, J. S., Baker, J. P., and Apperly, F. L. (1935). *Amer. J. med. Sci.*, **190,** 511.
Hunter, D., and Evans, W. (1929). *Proc. roy. Soc. Med.*, **23,** 224.
Jaffé, R. H. (1938). In *Handbook of Haematology*, edited by H. Downey, New York, **2,** 1122.
Junghagen, S. (1926). *Acta radiol., Stockh.*, **5,** 506.
Lieb, H. (1924). *Hoppe-Seyl. Z.*, **140,** 305.
—— (1927). *Ibid.*, **170,** 60.
—— and Mladenonic, M. (1929). *Ibid.*, **182,** 208.
Lowinger, L. (1935). *Folia haemat., Leipzig*, **53,** 126.
Mandlebaum, F. S. (1919). *Amer. J. med. Sci.*, **157,** 366.
——, and Downey, H. (1916). *Folia haemat., Leipzig*, **20,** 139.
Marchand (1907). *Münch. med. Wschr.*, **54,** 1102.
Mayo, W. J., and Mayo, C. H. (1935). *Coll. pap. Mayo clin.*, **27,** 558.
McConnell, J. S., Forbes, J. C., and Apperly, F. L. (1939). *Amer. J. med. Sci.*, **197,** 90.
Melamed, S., and Chester, W. (1938). *Arch. intern. Med.*, **61,** 798.
Merklen, P., Waitz, R., and Warter, J. (1933). *Ann. de Méd.*, **33,** 97.
Moncrieff, A. A. (1930). *Arch. Dis. Childh.*, **5,** 265.
Myers, B. (1937). *Brit. med. J.*, **2,** 8.
—— (1939). *Post-grad. med. J.*, **15,** 20.
Oberling, C., and Woringer, P. (1927). *Rev. franç. pédiat.*, **3,** 475.
Ogilvie, W. H. (1937). In Rowlands and Turner's *Operations of Surgery*, 8th edition, London, **2,** 519.
Pack, G. T., and Silverstone, S. M. (1938). *Amer. J. Surg.*, **41,** 77.
Packman, D. J. (1938). *Amer. J. Dis. Child.*, **56,** 248.
Pick, L. (1926). *Ergebn. inn. Med. Kinderheilk.*, **29,** 519.
—— (1933). *Amer. J. med. Sci.*, **185,** 753.
Potter, E. B., and Macrae, C. C. (1933). *Loc. cit.*, 92.
Reiss, O., and Kato, K. (1932). *Amer. J. Dis. Child.*, **43,** 365.
Rosenheim, O. (1914). *Biochem. J.*, **8,** 110.
—— (1916). *Ibid.*, **10,** 142.
Rowland, R. S. (1936). *Practice of Paediatrics*, ed. by J. Brennemann, Hagerstown, **3,** 77.
Schartum-Hansen, H. (1938). *Folia haemat., Leipzig*, **61,** 180.
Schlagenhaufer, F. (1907). *Virchows Arch.*, **187,** 125.
Schleussner, R. C., and Schnee, C. F. (1939). *N.Y. St. J. Med.*, **39,** 1665.
Sokolowsky, D. (1932). *Folia haemat., Leipzig*, **46,** 281.
Tannhauser, S. J. (1933). *Klin. Wschr.*, **12,** 49.
Thomson, R. H. S., and Wright, G. P. (1937). *Guy's Hosp. Rep.*, **87,** 30.
Webster, R. (1938). *Med. J. Austral.*, **2,** 22.
Welt, S., Rosenthal, N., and Oppenheim, B. S. (1929). *J. Amer. med. Ass.*, **92,** 637.
Worth, H. M. (1936). *Brit. J. Radiol.*, **9,** 753.

NERVE-CELL SWELLING OF THE JUVENILE AMAUROTIC FAMILY IDIOCY TYPE

ASSOCIATED WITH TUBEROSE SCLEROSIS IN AN INFANT AGED TWELVE MONTHS

BY

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This paper records the occurrence in the brain of an infant aged twelve months of tuberose sclerosis together with nerve cell changes of a type which, until recently, has been considered peculiar to the juvenile or Spielmeyer-Vogt variety of amaurotic idiocy. Pathological coincidences of this sort in the nervous system are rare and with the exception of Ostertag's (1925) description of infantile amaurotic idiocy associated with pachygyria and microgyria, I have been unable to find in the literature of either tuberose sclerosis or amaurotic idiocy a comparable example of double abnormality. Recently evidence has been brought forward suggesting that Hunter-Hurler's disease (gargoylism) is a member of the group of so-called lipoidoses (Ashby, Stewart and Watkin, 1937; Kressler and Aegerter, 1938), and it has been shown that the nervous system may be affected in a manner closely simulating juvenile amaurotic idiocy. There are reasons for believing that the condition now described differs materially from these two diseases, though the type of nerve cell change is very similar in all three. That such a pathological picture, hitherto reported only in much older individuals, should be found in fully developed form in an infant is sufficiently remarkable to deserve comment.

Case report

The patient, a male infant aged one year and ten days, was admitted to Stoke Park Colony on August 8, 1938.

Family history. Enquiry was welcomed by the parents, who were visited and a full family history obtained. This was entirely negative, but is summarized here for the sake of completeness. On the mother's side the patient's grandmother aged seventy is alive and healthy. The grandfather died aged sixty-four from 'pleurisy following influenza.' The paternal grandmother aged seventy-one is healthy. The paternal grandfather died from Bright's disease at the aged of fifty-nine. The father and mother are healthy, in comfortable circumstances and of superior mental type. They are non-Jewish and not blood relatives. The father was thirty-three and the mother thirty-one years old at the time of patient's birth. The mother has four healthy sisters iving. One sister died at the age of eighteen months, the cause of death being

' gastritis.' Two are married and one has a normal child. The father has two brothers both married. One has four healthy children, the other a single child also stated to be normal. The father also had an infant sister who died from ' meningitis ' aged two and a half years. He understands that the child was of normal mentality. The patient was the younger of two children, the elder sister aged four (seen) is a normal and well developed girl. There is no history of epilepsy or psychopathic traits in the pedigree and the mother knew of no relative with skin abnormalities or heart disease.

History prior to admission to colony. The pregnancy and labour were uneventful. The baby took the breast and was considered to be normal by the parents up to the age of about three months. Until this time development as judged by weight records was satisfactory. On looking back upon these early months, however, the mother now recalls that although reacting to sounds the baby did not seem to recognize her. Visual defect was not suspected until after an operation for circumcision, which was performed at four months. At that time nystagmus of the non-fixation type was first noticed. Teething started at four months. By six months physical and mental defect were obvious. At ten months the child could not sit up and the head tended to fall forwards. He did not grasp objects placed in his hands. Twitching of the side of the face was observed at eight months and generalized convulsions started two months later. These increased in frequency and at the time of the child's death at the age of twelve months averaged six a day. The blood Wassermann reaction was negative.

Examination on admission to the colony. A well-nourished baby; weight: 1 stone 8 lb. Height: 2 ft. 7 in. The upper and lower incisors were present. Apart from a rapid rate no cardiac abnormality was found. There was no enlargement of thyroid, liver or spleen. The infant was unable to hold up his head, sit up or stand. He paid no attention to visual stimuli. The head was large: length, 166 mm.; breadth, 134 mm.; height, 127 mm. The facies was not that of gargoylism.

NERVOUS SYSTEM. Muscle tone was not increased in the limbs. The tendon reflexes were equal on both sides and not exaggerated in arms and legs. The abdominal and cremasteric reflexes were not obtained. There was a variable Babinski sign on both sides. The pupils were equal and reacted to light.

Progress. During the first three days after admission he averaged six fits a day. The fits started with a scream, followed by twitching of the limbs for several seconds. On the fourth day his colour became poor, the temperature rose to 100° F., and an impaired percussion note and diminished breath sounds were detected over the left base. The heart sounds were rapid and feeble. No improvement in the general condition occurred, and the next day death took place.

Post-mortem report. At the autopsy signs of early broncho-pneumonia were present in the lower lobe of the left lung, but they were not considered sufficient to have accounted for death in a normal child. Small areas of atelectasis were found in the lungs. In the heart numerous small greyish areas, lying flush with the adjacent muscle tissue, were observed in the walls of both ventricles and auricles, in the interventricular septum and in some of the papillary muscles. There was no valvular abnormality. The spleen, liver, suprarenals and other visceral organs appeared normal.

On removing the calvaria, which was of normal thickness, the dura and leptomeninges showed no abnormality, but the brain consistency was much denser than usual, suggesting a diffuse cortical sclerosis.

After fixation in formol saline the weight of the brain was 1,307 grammes. A closer inspection of the cerebral hemispheres after stripping showed that

the cerebral cortex was extensively affected by tuberose sclerosis, for although all parts of the brain seemed tougher than usual to palpation, portions of the gyri showed the whitish, hard, discrete patches characteristic of the condition. The width of the gyri varied abnormally, those affected by tuberose sclerosis being sometimes unusually massive; but the general impression given was that of a richly convoluted brain. Although no gross malformation of gyral pattern was present, a few minor abnormalities were seen, the left superior temporal sulcus being short and irregular, the right Rolandic sulcus being in two parts and the right angular and supramarginal gyri ill-defined.

The left cerebral hemisphere was reserved for microscopical examination. On section the lateral ventricle was found to be dilated, especially in the posterior horn. Small subependymal tumours and 'candle-gutterings' were attached to the caudate nucleus and thalamus.

Microscopical examination of the visceral organs

The LUNGS showed an early broncho-pneumonic process of limited extent and also areas of atelectasis.

The BRONCHIAL LYMPH NODES contained small deposits of neutral fat, but not in abnormal amount.

In the SPLEEN groups of endothelial cells enclosed material having the staining properties and solubility of neutral fat. After treatment with chloroform, minute granules, staining yellow with scharlach R, were found in some of the endothelial cells. Similar findings occurred in normal control material. There were no foam cells visible.

The LIVER showed an unusual degree of fatty infiltration, small closely packed droplets of fat being uniformly present in all zones of the lobules. No scharlach-staining material remained after treatment with alcohol. No foam cells were seen.

The KIDNEYS were normal.

In the HEART the small grey areas observed macroscopically proved to be rhabdomyomata consisting of primitive muscle cells showing a loose texture (fig. 1) in which with higher magnification transverse striation was frequently seen (fig. 2).

Microscopical examination of the nervous system

CEREBRAL CORTEX. Nineteen representative areas were examined from the left cerebral hemisphere.

NERVE CELLS. A varying degree of disorderly arrangement of nerve cells was present in the tuberose parts of the gyri, but generally speaking there was no gross upset of cytoarchitectonics. A conspicuous feature of most of the sections were large nerve cells of abnormal shape contrasting sharply with the small size of their neighbours (fig. 3). Groups of these giant cells were frequently seen in the deeper cortical layers. The nerve cells for the most part stained poorly with cresyl violet owing to a poverty of Nissl bodies. With this stain it was possible to recognize, particularly in the larger pyramidal cells, a pyriform distension of the cell body with a finely granular substance, the nucleus and Nissl bodies being pushed to the apex of the cell. The swollen cell body often showed a finely reticulated appearance. These changes were much more easily recognized in Bielschowsky preparations. The condensed neurofibrillae forming a peripheral ring round the distended cyton were demonstrated by this method, the pathological picture being typical of juvenile

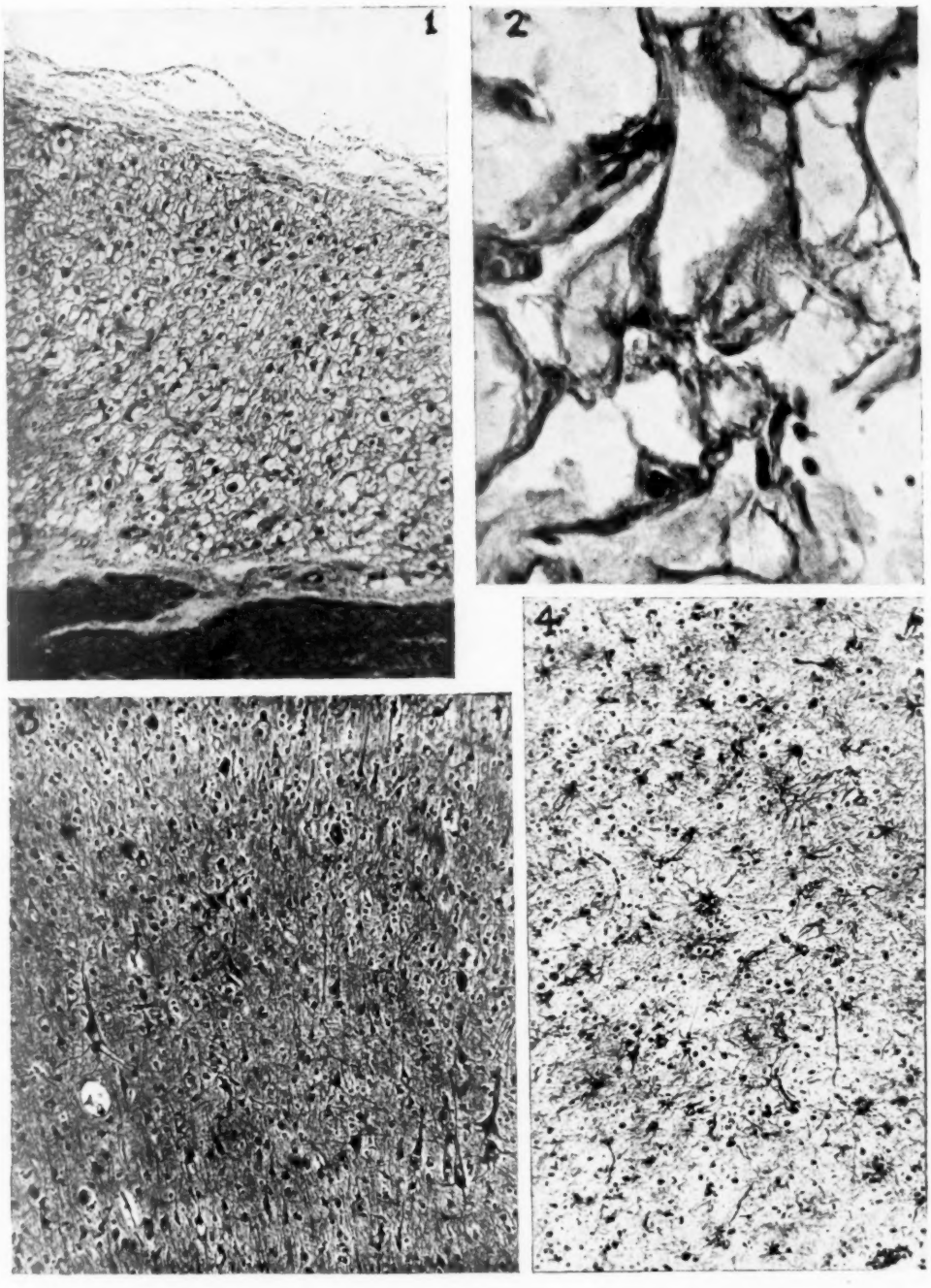


FIG. 1.—Rhabdomyoma of heart showing primitive muscle cells. (H. and E. ; × 36.)

FIG. 2.—Rhabdomyoma of heart showing striped muscle fibres. (H. and E. ; × 450.)

FIG. 3.—Large abnormal nerve cells in a tuberose portion of the second frontal gyrus. (Bielschowsky's stain ; × 80.)

FIG. 4.—Abnormal astrocytes in tuberose portion of second temporal gyrus. (Hortega's method for astrocytes; × 80.)

amaurotic idiocy (fig. 5). Swelling of the cell processes was not seen save in one or two doubtful instances. The ubiquitous distribution of these granular inclusions was obvious in sections stained by scharlach R, a varying amount of pinkish-orange substance, usually in the form of fine granules, being present in almost every cell. The large abnormal cells shared in this change (fig. 6). This distension of the nerve cells with scharlach-staining material was a feature of every cortical area examined and no layer was exempt. There was much variability in the degree of affection of the finer pyramids, some appearing grossly swollen, others containing but few granules. This intracellular granular substance had the following staining reactions: cresyl violet usually failed to colour the granules, but sometimes the larger deposits stained pink. There was no metachromatic staining with toluidin blue. Scharlach R gave a light pink or orange colour. There was no blackening with osmic acid, either with or without chromication. Nile blue stained the deposit deep blue. Using the Kultschitsky-Pal method greyish granules appeared in the nerve cells after two days and were well defined and darker in colour after three days in the mordant. The solubility of the deposit was tested and it was unaffected by ethyl alcohol, methyl alcohol, acetone, ether, benzine, or hot and cold chloroform. Immersion in these solvents overnight seemed rather to improve the penetration of the scharlach, the granules staining a brilliant orange. The substance was present in undiminished amount in celloidin sections. Prolonged immersion at 40° C., or boiling for five minutes in 20 per cent. trichloracetic acid did not affect the solubility. The reaction to polarized light was also tested. The granules were not doubly refractile. No extra-cellular doubly refractile deposits were seen in frozen or celloidin sections of cortex or thalamus.

MYELIN. The cortex was poor in myelin, the radial bundles being thin. The stria of Gennari could not be identified in myelin preparations. In the tuberose parts of the cortex myelin was often almost absent in the grey, and sometimes grossly reduced in the central core of white matter, only a few fine fibres being visible in each microscopic field. Generally speaking, however, the subcortical white matter appeared well myelinated.

NEUROGLIA. In all sections examined there was a heavy, uniform fibrillary gliosis in grey and white matter, denser in the tuberose areas, but present also in the macroscopically less sclerosed areas. Metallic impregnation methods demonstrated several sorts of abnormal astrocytes, big fibrillary types with fleshy cell bodies and numerous coarse wavy processes predominating (fig. 4). Here and there astroblastic types were seen. Giant cells of round or oval shape with peripheral nucleus and usually without processes were scattered throughout the different cortical layers and were especially numerous round blood vessels in the white matter of the gyri. Occasional giant cells or more obviously astrocytic type having short flesh processes could be identified. More rarely, a larger type of elongated giant cell with a leash of long processes at either end of the cell body was seen. No lipoid granules were found in the astrocytes, and the giant cells of glial type did not share in the granular change of their neuronal prototypes.

MICROGLIA. Compound granular corpuscles were not numerous in the cortex, but most sections showed some, usually near the vessel walls. At this site the compound granular corpuscles contained neutral fat, but elsewhere gitter cells filled with a substance having staining properties and insolubility identical with those of the granular deposit in the nerve cells were commonly found.

BLOOD VESSELS. Heavy neutral fat deposits in the vessel walls were common, especially in those of the subcortical white matter. The vessels in the sclerotic parts of the cortex showed proliferation of mesenchymal fibrils.

BASAL GANGLIA. Distension of nerve cells with insoluble granules was a conspicuous feature, the caudate nucleus and putamen being less grossly affected

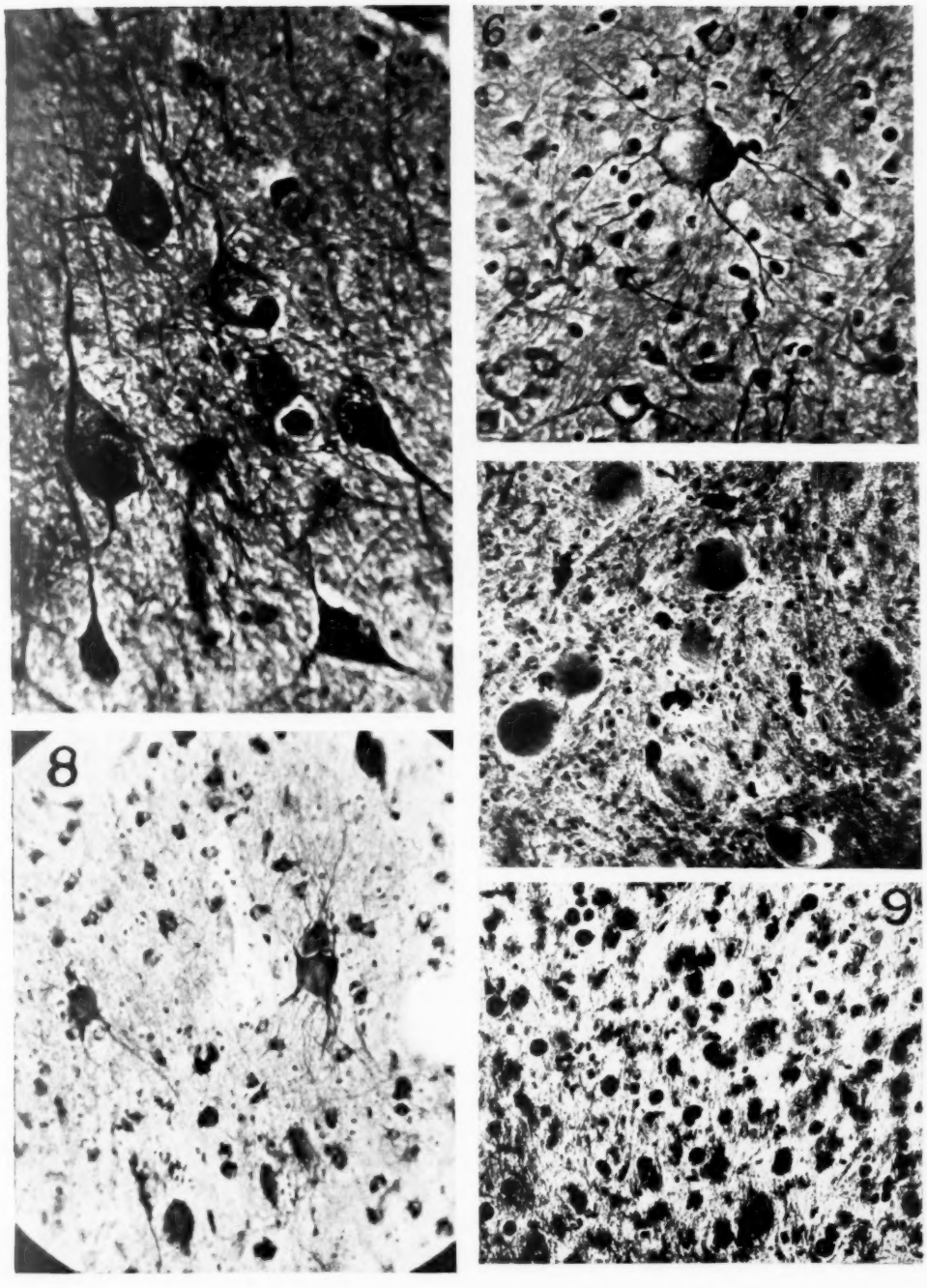


FIG. 5.—Nerve-cell swelling resembling that of juvenile amaurotic idiocy. Supramarginal gyrus layer V. (Bielschowsky's stain ; × 450.)

FIG. 6.—Giant cell of neural type affected by granular swelling. First frontal gyrus. (Bielschowsky's stain ; × 270.)

FIG. 7.—Granular swelling in nerve cells of dentate nucleus. Compound granular corpuscles. (Scharlach R. and Haematoxylin ; × 270.)

FIG. 8.—Giant cells of glial origin in thalamus subjacent to subependymal tumour. (Cajal's gold sublimate method ; × 180.)

FIG. 9.—External geniculate body. Section has been treated with boiling chloroform and shows compound granular corpuscles filled with insoluble substance. The granules in the nerve cells are visible as larger and less dense aggregations. (Scharlach R. and haematoxylin ; × 180.)

than the thalamus and globus pallidus, where swelling of cells to two or three times their usual size was seen. These large cells stained a pink colour with scharlach and pink staining with cresyl violet was usual. In Bielschowsky preparations the thalamic cells often showed a reticulated appearance. Giant cells of the rounded form seen in the cerebral cortex were present in the thalamus, caudate nucleus and putamen. In all these areas there was a well-marked fibrillary gliosis, most intense in the thalamus and affecting both white and grey matter. The larger fibre tracts were well myelinated, but the finer fibres in the grey matter seemed reduced in number, particularly in the putamen. Gitter cells containing neutral fat and insoluble substance were numerous in the thalamus, and the walls of the blood vessels contained much neutral fat.

The EXTERNAL GENICULATE BODY showed changes similar to those in the thalamus, but in accentuated form (fig. 9). There appeared to be considerable cell loss and compound granular corpuscles were numerous.

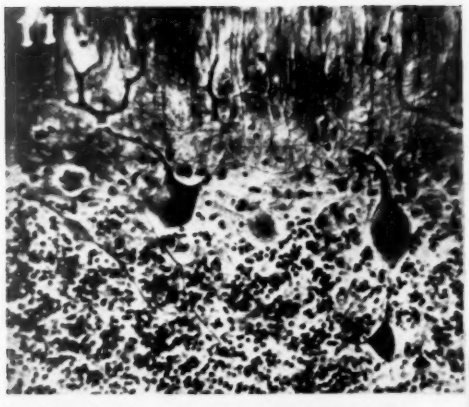
SUBEPENDYMAL TUMOURS. A tumour the size of a large pea was attached to the thalamus and caudate nucleus. It was composed of leashes of coarse glial fibres in the interstices of which were seen groups of giant cells resembling those found elsewhere, but usually having processes at both poles. The central part of the tumour was highly vascular, many of the vessels being calcified. Large calcium deposits were present. The junction of this tumour with the basal ganglia was marked by a broad layer of fine neuroglial fibres, and the transition zone between this band and the parenchyma of the thalamus was particularly rich in giant cells (fig. 8). As in the cortex, these giant cells did not share in the granular change of the neurones. Similar round circumscribed tumours of coarse glial fibres and giant cells were found at the junction of putamen and globus pallidus and in the pons subjacent to the fourth ventricle.

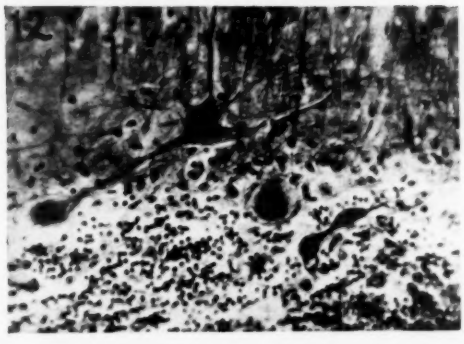
CEREBELLUM. The Purkinje cells of the vermis and lateral lobes all showed moderate swelling of the cell body with insoluble material staining orange-pink with scharlach. Their dendrites often appeared thickened and frequently definite distension with scharlach staining material was observed (fig. 12). Axonal torpedoes were common (fig. 11 and 12). An occasional Purkinje cell of abnormally large proportions was seen (fig. 13). No gross atrophy of Purkinje or granular cells was observed and the latter seemed unaffected by the granular deposit. The basket and the tangential fibres were well preserved. There was a marked fibrillary gliosis in the white matter and the Bergmann fibres of the molecular layer were thickened and proliferated (see fig. 10). Myelinization was normal. Gitter cells containing fat or insoluble material were present in small numbers in the molecular and granular layers and the vessels in the granular layers contained excess of neutral fat.

The DENTATE NUCLEUS showed no atrophy, but all nerve cells were grossly swollen (see fig. 7). There was a heavy fibrillary gliosis around the cells and in the hilum. Compound granular corpuscles were numerous.

MIDBRAIN, PONS, MEDULLA. All nerve cells were affected by the granular change, the inferior olives and pontine nuclei particularly so (fig. 14). The larger fibre bundles, including the pyramidal tracts, were well myelinated, but the nuclear masses showed some poverty of finer fibres. There was a well-marked gliosis of fibrillary type around the affected nerve cells. Gitter cells were present in the inferior olives.

SPINAL CORD. Most of the nerve cells in the cervical cord showed granular distension but a few of the anterior horn cells appeared unaffected. A mild gliosis was present in the grey matter. There was no sclerosis or demyelinization in the fibre tracts. The lateral columns, however, stained less intensely with the Kultschitsky-Pal method than the rest of the cord.





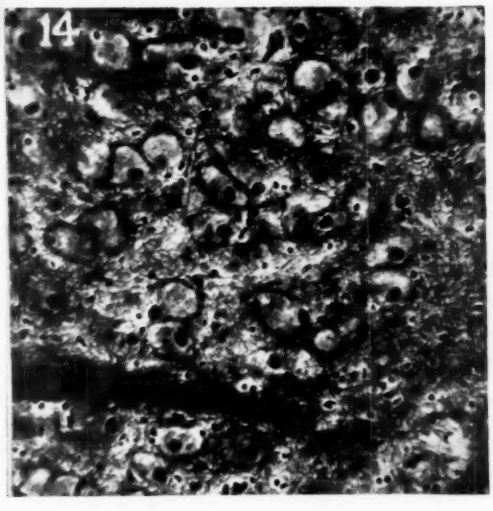


FIG. 10.—Lateral lobe of cerebellum. Thickening and proliferation of Bergmann's fibres. A few swollen dendrites of the Purkinje cells are visible in the molecular layer. (Hortega's method for astrocytes ; × 60.)

FIG. 11.—Cerebellum. Axonal torpedoes. Purkinje cells show slight granular swelling. (Bielschowsky's stain ; × 180.)

FIG. 12.—Cerebellum. Swelling of dendrite of Purkinje cell. (Bielschowsky's stain ; × 180.)

FIG. 13.—Giant Purkinje cell. (Bielschowsky's stain ; × 180.)

FIG. 14.—Swelling of nerve cells of pontine nuclei with surrounding fibrillary gliosis. (Hortega's method for astrocytes ; × 180.)

Discussion

Many of the pathological features described above are those of tuberose sclerosis and this aspect of the case requires little comment. The macroscopically sclerosed areas in the cortex, the subependymal nodules, widespread glial abnormalities, disturbed architechtonics and giant cells of neural and glial type leave no doubt as to the nature of the condition, and confirmatory evidence is furnished by the association of cardiac rhabdomyomata, a not uncommon feature of the syndrome of epiloia. Clinically, as in the present case, the diagnosis of tuberose sclerosis may be impossible in an infant suffering only from epilepsy and mental defect. Adenoma sebaceum is seldom present in early life and the other skin abnormalities found in the fully developed form of the disease may be absent. Blindness has been mentioned as a suggestive sign by Globus and Selinsky (1935), but it does not appear to be common in the recorded cases. Since tuberose sclerosis is inherited in all probability as a single dominant gene (Gunther and Penrose, 1935; Penrose, 1936) it is not unusual to find other affected relatives, but in sporadic cases such as this one, in which the disease presumably arises by mutation in a parent, the family history gives no diagnostic clue. Unfortunately in the present instance the infant died before an ophthalmoscopic examination had been made, so that it is impossible to say whether the rare phakomata were present in the retina. Moreover, an examination of the fundus might have helped considerably in the interpretation of the other pathological aspect of this case, namely, the granular swelling of the nerve cells, for, as is well known, the infantile type of amaurotic idiocy does occur, though less frequently, in non-Jewish families.

From the histological point of view it is improbable that in this case the nerve-cell swelling was due to infantile amaurotic idiocy, although the possibility exists that the coincidental tuberose sclerosis may have modified the expression of the disease in a radical manner. In general, the degree of affection of the nerve cells was more akin to that seen in the juvenile type. Ballooning of the cell processes usual in the infantile form was not seen save in one or two doubtful instances. The colouring of the granular inclusions by scharlach and haematoxylin was orange rather than the rosy-red of Tay-Sachs' disease. The gross myelin defects and status spongiosus commonly seen in Tay-Sachs' disease were not present, such myelin defects as were noted being no more than are usual in tuberose sclerosis. The most important distinction of all, however, lies in the insolubility of the granular deposit. The pre-lipoids of infantile amaurotic idiocy are soluble in the more powerful lipoid solvents, whereas the granules of the present case resisted boiling chloroform and celloidin embedding. A corollary of this insolubility of the nerve-cell inclusions is probably seen in the absence of scharlach-staining granules in the astrocytes. In the infantile form of amaurotic idiocy lipoid granules in the cell bodies of the macroglia are conspicuous and regressive changes are common. In the juvenile type, in which the nerve-cell lipoid is only soluble in hot solvents or after prolonged treatment in the cold, the lipoid content of the astrocytes is often inconspicuous. The absence of lipoid in the astrocytes of the present case would thus appear to

reflect the difficulty of assimilating a yet more insoluble substance. In this connexion it is of interest to note that the compound granular corpuscles in this brain contained both insoluble material (as in the nerve cells) and neutral fat. It is thus probable that a reduction into simpler forms may have been effected in the microglial cells themselves. Apart from this extreme degree of insolubility of the granular inclusions the pathological findings closely resemble those of the juvenile or Spielmeyer-Vogt variety of amaurotic idiocy. The cerebellar changes in particular are characteristic of that type of the juvenile form in which gross atrophy is absent. Yet, as is well known, this form of the disease manifests itself only after several years of normal development and unless once more the hypothesis is to be evoked that the coincidental tuberose sclerosis has modified the customary course of the disease it is inconceivable that an infant of one year should be suffering from a condition genetically identical to juvenile amaurotic family idiocy.

It is more difficult to rule out the possibility that this case is an early form of Hunter-Hurler's disease, for although seventeen cases have been reviewed from the clinical standpoint by Ellis, Sheldon and Capon (1936), only four examples of the disorder have been examined histologically (Tuthill, 1934, one case; Stewart and co-workers, two cases; Kressler and Aegerter, one case). It is true that in the present case there was nothing clinically to suggest gargoylism, but the characteristic osseous abnormalities are not necessarily visible at so early an age. Enlargement of liver or spleen, absent in this case, is not a constant feature of the disorder. A point of greater diagnostic significance is the congenital or early infantile clouding of the cornea often present in the Hunter-Hurler syndrome; this also was absent in the present case. From the histological point of view there are differences between the findings in this brain and those of Tuthill and Stewart.* Extracellular deposits of doubly refractile lipoid were not found as in Stewart's first case. The intensity of the pathological process in the cerebellum appears to be greater in the present case than in the recorded examples of gargoylism. Also the degree of general fibrillary gliosis was much more pronounced. Although this last observation loses some of its significance owing to the presence of tuberose sclerosis it may be said that whereas in tuberose sclerosis abnormal glial cells are usually present in non-tuberose areas, a generalized fibrillary gliosis of the intensity encountered here is distinctly unusual. From this comparison it would appear that there is little or no positive evidence in favour of this case being an early example of gargoylism. The one feature the two disorders have in common is the ubiquitous distension of the nerve cells with insoluble granules, but this seems hardly sufficient support for the view that the conditions are identical, particularly since it is uncertain whether in Hunter-Hurler's disease a degree of nerve-cell affection comparable with that of the present case occurs as a congenital or early infantile phenomenon.

* The nervous changes in the case described by Kressler and Aegerter are not reported in detail. Apart from the failure of the infiltrating substance to stain, the authors considered their findings identical with those in Stewart's first patient.

The extreme insolubility of the nerve-cell deposits raises a difficulty in nomenclature, for the name ' lipoid ' seems under the circumstances inappropriate. To account for the relative insolubility of the granules in juvenile amaurotic idiocy it has been suggested that a combination of lipoid and protein has taken place, but if this is so in the present case the union must have been singularly stable, since it resisted the action of hydrolysis. In view of the non-involvement of the reticulo-endothelial system in liver, spleen and lymph nodes it would also appear unjustifiable to attempt to force this case by analogy into the group of ' lipoidoses.' Certain features of this case appear to be unique and cannot readily be brought into line with previously described disorders.

Summary

The post-mortem examination of an infant of twelve months showed tuberose sclerosis of the brain, rhabdomyomata of the heart and nerve-cell swelling resembling in the main that of juvenile amaurotic family idiocy. The granular inclusions in the nerve cells were insoluble in lipoid solvents. No evidence of a general disturbance of lipoid metabolism was found. A comparison between the clinical and pathological features of this case with those of amaurotic idiocy and Hunter-Hurler's disease suggested that the condition is distinct from these previously described disorders, but its etiology remains obscure.

REFERENCES

Ashby, W. R., Stewart, R. M., and Watkin, J. H. (1937). *Brain*, **60**, 149.
Ellis, R. W. B., Sheldon, W., and Capon, N. B. (1936). *Quart. J. Med.*, **5**, 119.
Globus, J. H., and Selinsky, H. (1935). *Amer. J. Dis. Child.*, **50**, 963.
Gunther, M., and Penrose, L. S. (1935). *J. Genetics*, **31**, 413.
Kressler, R. J., and Aegerter, E. E. (1938). *J. Pediat.*, **12**, 579.
Ostertag, B. (1925). *Arch. Psychiat. Nervenkr.*, **75**, 355.
Penrose, L. S. (1936). *Ann. Eugen, Camb.*, **7**, 16.
Tuthill, C. R. (1934). *Arch. Neurol. Psychiat., Chicago*, **32**, 198.

THE BLOOD CHOLESTEROL CONTENT IN CHILDHOOD

BY

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Although a knowledge of variations in the cholesterol content of the blood has not been shown to be of direct value in clinical medicine, the fact that this substance forms the basis of many of the essential hormones and vitamins gives it an important place in the chemistry of living processes. It has been shown that cholesterol, bile acids, vitamin D and the male and female hormones have a common carbon skeleton (Gainsborough, 1935). Ruzicka and his colleagues (quoted by Callow and Parkes, 1937) have prepared androsterone from it, and Vollmer and others (1927) have shown that vitamin D can be formed from it by irradiation. From such work it is apparent that cholesterol must rank as one of the important constituents of the living body.

The blood cholesterol content in health

The blood cholesterol content has been extensively studied both in healthy adults and children, but the results have shown a wide range of variation. In table 1 the figures recorded by different workers for healthy adults are shown. These figures range from 100 mgm. per cent. to 392 mgm. per cent. In healthy

TABLE 1

THE BLOOD CHOLESTEROL CONTENT IN NORMAL ADULTS

AUTHOR	CHOLESTEROL RANGE OF VALUES (MGM. PER CENT.)	MATERIAL EXAMINED	METHOD
Grigaut (1913) ..	140–190	Serum	Grigaut
Denis (1917) ..	167–255	Blood	Bloor's modification of Autenrieth-Funk
Campbell (1924) ..	110–190	Plasma	Myers and Wardell
Teilum (1935) ..	150–230	Serum	Rappaport and Engelberg
Sperry (1936b) ..	146–392	Plasma	Schönheimer and Sperry
Schube (1937) ..	100–200	Blood	Myers and Wardell

* Part of this work was performed during the tenure of a Muirhead Research Scholarship.

TABLE 2

THE BLOOD CHOLESTEROL CONTENT IN NORMAL CHILDREN

AUTHOR	AGE IN YEARS	CHOLESTEROL RANGE OF VALUES (MGM. PER CENT.)	MATERIAL EXAMINED	METHOD
Baranski (1926) ..	8/365–12	125–170	Serum	Grigaut
Manicatide et al. (1927)	2/52–4/12	100–180	Serum	Grigaut
Baylac and Sendrail (1928)	1/12–15	95–169	Serum	Grigaut
Sylvestre (1929) ..	1/12–14	80–160	Serum	Grigaut
Gordon and Cohn (1928)	1/52–6	85–190	Serum	Bloor
Acũna and Winoçur (1931)	3/365–15	50–230	Blood	Sackett's modification of Bloor
Kaiser and Gray (1934)	5–16	108–201	Serum	Bloor
Molitch and Poliakoff (1936)	8–18	81–204	Serum	Reinhold's modification of Sackett
Ward (1931)	6–13	125–158	Blood	Leiboff
Sperry (1936a) ..	1/365–25/365	71–190	Plasma	Schönheimer and Sperry
Offenkrantz and Karshan (1936).. ..	3/12–12	174–186	Serum	Schönheimer and Sperry
Gortz (1937)	1/365–12	108–166	Blood	Gortz
Present series (1938) ..	1/12–12	96–134	Blood	Leiboff

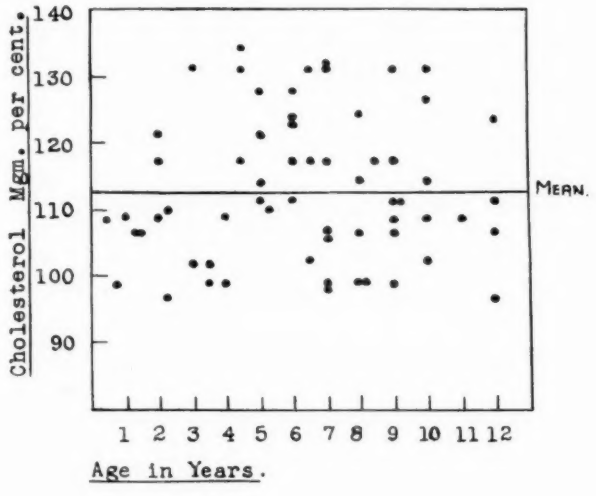
children a similar, though rather less wide, range of variations is shown (table 2). It is difficult to account for these discordant results. They cannot be explained by the use of different methods of estimation, for even one worker using the same technique in all experiments may get gross variations from case to case. Neither can these variations be attributed to difference in diet. This question has been studied by many workers (Chaikoff, McGavack and Kaplan, 1934; Blottner and Fitz, 1934; Blottner, 1935; Wilson and Hanner, 1934; and Bloor, 1916 and 1933). Although there is still some lack of agreement, a large number of those who have studied the subject believe that cholesterol variations are quite independent of food intake. Furthermore, the cholesterol content does not appear to vary with age. In the present series, in which the ages ranged from a few months to twelve years, no significant variations in the blood cholesterol content could be detected (chart I).

In view of this, and before attempting to study changes in blood cholesterol content occurring in disease, it was thought essential to determine the normal range of variation in healthy children, excluding as far as possible extraneous influences. Owing to the undesirability of withdrawing more than a small quantity of blood from young children, a modification of the micro-method of Leiboff (1924) was employed, which entails the withdrawal of only 0·2 c.c. of blood. The estimations were carried out on oxalated whole blood and were made after a four or five hours' fast. Sixty-two apparently healthy children who had not suffered from any recent illness were studied. The majority were admitted to hospital on account of some surgical condition, such as congenital dislocation of the hip, talipes or hernia, and a few were out-patients attending

the dental clinic; cases of alveolar abscess were excluded. All the estimations were made prior to any surgical procedure. The results do not show such a wide range as those recorded by some other workers. The highest figure obtained was 134 mgm. per cent. and the lowest 96·0 mgm. per cent. (chart I) The average figures for various ages show only minor differences. No significant difference could be found between the sexes; the average for males was 114·1 mgm. per cent. and for females 110·9 mgm. per cent. It has been claimed

CHART I

THE BLOOD CHOLESTEROL IN NORMAL CHILDREN



that there is a seasonal variation in the blood cholesterol content (Currie, 1924; Kaiser and Gray, 1934), but the present results do not show this. The average figure for the winter months was 110·7 mgm. per cent. and for summer months 114·8 mgm. per cent. It would appear, therefore, that using the technique described above, the normal values for children up to the age of twelve years lie between 96·0 mgm. per cent. and 134 mgm. per cent., and that these figures are not materially influenced by diet, age, sex or season.

The blood cholesterol in disease in childhood

Most authorities agree that there is diminution in the blood cholesterol content in acute infections, in parenchymatous liver diseases and in hyperthyroidism, whereas in nephrosis, obstructive jaundice and in hypothyroidism it is increased. In the present paper a study of the blood cholesterol content in pneumonia and empyema, acute rheumatism and acute nephritis has been made. These diseases represent types of acute infections. In addition, series of cases of nephrosis and obstructive and haemolytic jaundice have been investigated.

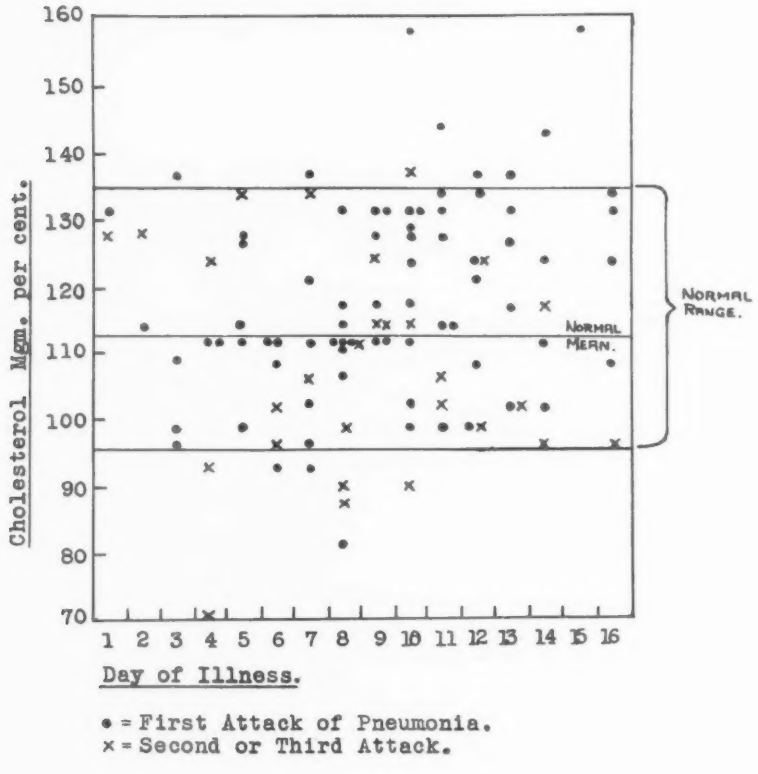
Pneumonia and empyema. There is fairly general agreement that in pneumonia there is diminution of the blood cholesterol content during the acute stage of the disease (Kipp, 1920; Chauffard et al., 1920; Steiner and Turner, 1940), and Chauffard and Steiner with their co-workers claim that there is hypercholesterolaemia during convalescence. Similar results have been found by most of those who have studied the question in children (Lesné et al., 1929; Stroesser, 1936). On the other hand, Simonini (1933) and Goldbloom and Gottlieb (1927) have failed to confirm these results.

The present series comprises sixty-two children suffering from acute lobar or broncho-pneumonia. Thirty-four of these were under two years of age. In many of the patients the cholesterol was estimated two, three and four times a week during the course of the illness and convalescence. Though in the great majority of the cases the cholesterol values lay within normal limits, higher values tended to occur during convalescence than during the acute stage of the disease (charts II and III). This was specially noticeable in children under two years of age. Children under two years of age who were suffering from a second or third attack gave low results and in them there was not the same

CHART II

THE BLOOD CHOLESTEROL IN PNEUMONIA

CHILDREN OVER TWO YEARS

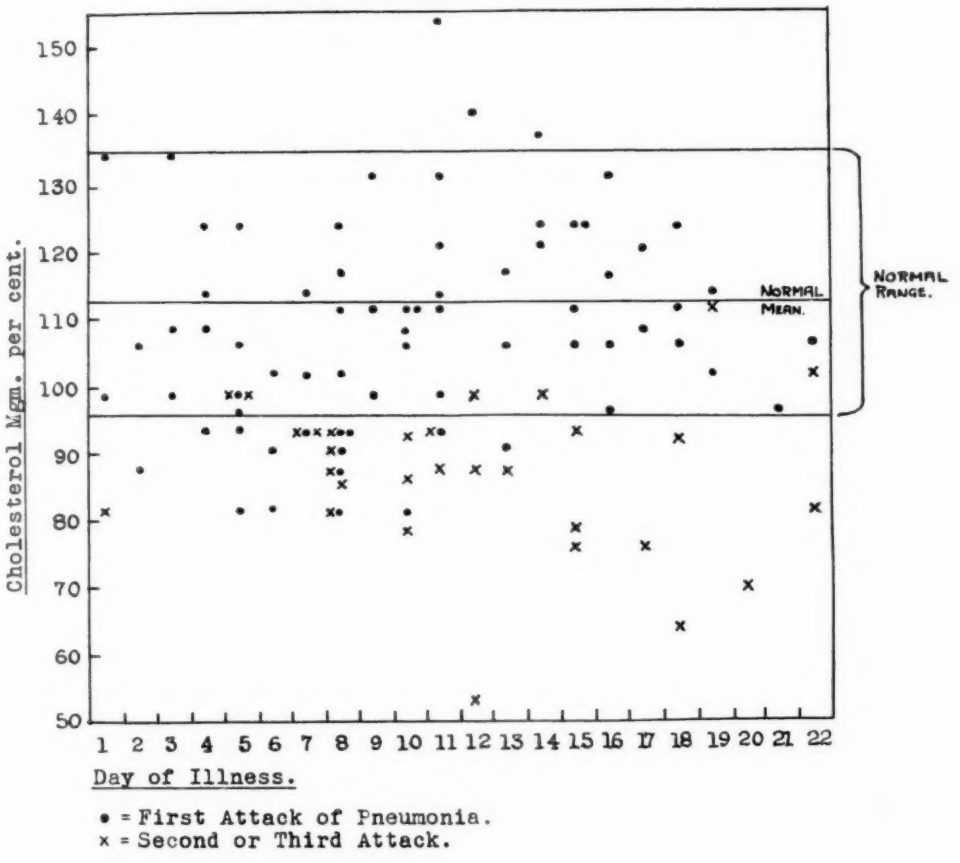


tendency for the values to rise with convalescence. It is difficult to assess the significance of this, though it is possible that recurrent infection may cause a lowering of blood cholesterol in the same way that, as shown by Grigaut (1913), it is lowered in prolonged acute infections. No correlation between the extent of lung involvement and the height of the blood cholesterol could be detected. For example, in one patient the cholesterol was found to be 111·5 mgm. per

CHART III

THE BLOOD CHOLESTEROL IN PNEUMONIA

CHILDREN UNDER TWO YEARS



cent. twenty-four hours before death, although at autopsy an extensive suppurative broncho-pneumonia was revealed.

Nine cases of pneumococcal empyema were examined. In six of these the cholesterol value was low, but in one it was high. Four of the children died, and of these two showed hypocholesterolaemia and in two the cholesterol value was within normal limits. In the cases in which there was long-continued sepsis there did not appear to be any tendency for lower values to appear than in those in which resolution was rapid.

Although these results do not show such striking alteration from the normal as those of some other authorities, there seems little doubt that there is diminution in the blood cholesterol content during the acute stage of pneumonia and in a considerable proportion of cases of empyema. Only in a few cases, however, has it been possible to demonstrate hypercholesterolaemia during the convalescent stage.

The rheumatic infection of childhood. References to juvenile rheumatism in the literature on cholesterol are comparatively scanty, and the few observations published on the subject are somewhat conflicting.

Goldbloom and Gottlieb (1927) made their determinations on whole blood and found hypercholesterolaemia in rheumatic fever. Their work does not appear, however, to have been substantiated by more recent investigators. Ward (1931) and Kaiser and Gray (1934), using whole blood and plasma respectively and employing different methods of estimation, obtained results which differed little from their own normal figures. Offenkrantz and Karshan (1936) found the serum cholesterol within normal limits in acute rheumatism. Lesné et al. (1929) observed normal or slightly elevated values in Sydenham's chorea.

The present series comprised sixty-three cases of juvenile rheumatism. In some patients it has been possible to observe the blood cholesterol values from the initial acute stage for a period of a year or longer. Nine cases were examined during an attack of acute arthritis or within a few days of the subsidence of the acute arthritic manifestations. The blood cholesterol content during this acute stage ranged between 90·1 mgm. per cent. and 108·5 mgm. per cent. (average 100·3 mgm. per cent.) and with convalescence it rose to an average of 109·1 mgm. per cent. (table 3). During the subsequent course of convalescence the cholesterol values all tended to rise. There were, however, in a considerable

TABLE 3

THE BLOOD CHOLESTEROL IN ACUTE RHEUMATISM

CASE NO.	AGE IN YEARS	CHOLESTEROL MGM. PER CENT. NUMBER OF DAYS AFTER THE ONSET OF ARTHRITIS			
		LESS THAN 7	14	21	28
2	7	96·0	117·2	102·3	—
3	8	98·9	105·7	111·5	—
4	9	105·7	105·7	117·2	—
5*	10	108·5	114·3	134·0	131·0
7	11	90·1	96·0	102·3	111·5
8	12	96·0	117·2	111·5	111·5
9	8	93·1	114·3	102·3	117·2
10	12	108·5	102·3	114·3	—
11*	8	105·7	—	117·2	114·3
Average		100·3	109·1	112·5	117·1

* Second attack of rheumatism.

number of cases marked oscillations, and it was noted that a fall in the cholesterol value was in many cases associated with tonsillectomy or dental extraction. No consistent changes could be observed with the onset of carditis, though in three of six cases of pericarditis low values were obtained and in four cases of endocarditis with decompensation low values were found in two. In spite of the fact that the development of rheumatic nodules is generally considered to indicate activity of the disease, their presence did not seem to lead to any alteration in cholesterol values.

Serial determinations were made in nineteen children with chorea. None of these showed abnormally low cholesterol values, though in about half of the cases it rose as convalescence progressed.

From these results it seems that in the acute stage of rheumatic arthritis there is frequently a lowered blood cholesterol content which rises as convalescence proceeds and that in pericarditis and cardiac decompensation low values may be found. In the other manifestations of rheumatism such as nodules and chorea no consistent changes could be observed. It seems probable that the initial low blood cholesterol levels found in the acute arthritic stage of the disease are the result of an acute febrile illness and are analogous to the low values which occur in pneumonia. The rheumatic infection, however, in its chronic stages does not appear to influence the blood cholesterol level.

Nephritis. Twelve cases of acute nephritis were studied. Eight of these were observed in the early stages ; they all, save one (case 17), showed low or normal values and within a week of the subsidence of fever the cholesterol rose to above the level observed during the febrile period (table 4). It was also

TABLE 4

THE BLOOD CHOLESTEROL IN ACUTE NEPHRITIS

CASE NO.	TEMPERATURE	CHOLESTEROL MGM. PER CENT.		INTERVAL BETWEEN (*a*) AND (*b*) IN DAYS	OEDEMA
		(*a*) DURING FEVER	(*b*) AFTER FEVER		
1	99·4	102·3	136·9	4	++
6	99·0	98·9	127·6	7	—
8	99·4	128·1	131·0	2	
11	100·6	102·5	131·0	4	+
17	99·6	157·4	178·1	3	+
19	102·2	114·3	150·6	2	+
22	99·0	96·0	131·0	6	
23	100·0	87·3	111·5	5	+

observed that an intercurrent infection occurring during the course of the illness produced a diminution in the blood cholesterol. In one child a moderately severe attack of diarrhoea led to a fall of the cholesterol from 164·3 mgm. per

cent. to 115·5 mgm. per cent. within twenty-four hours. In another child an upper respiratory infection with a rise in temperature to 102° F. was associated with a fall of cholesterol from 131 mgm. per cent. to 117 mgm. per cent. It is probable that the increase in the cholesterol values found during convalescence in these eight cases was the result of subsidence of the infection which gave rise to the nephritis.

The influence of oedema has also to be reckoned with. It has been claimed on the one hand that in the presence of oedema the blood cholesterol is invariably raised (Maxwell, 1928), whilst on the other hand it is asserted that the occurrence of lipaemia and oedema in nephritis is only a coincidence (Peters and van Slyke, 1931). Oedema occurred in seven cases of the present series. In four of these the cholesterol was low or within normal limits during the oedematous phase and rose with the disappearance of oedema ; in three the cholesterol was above normal while oedema was present, but with its subsidence there was a fall to approximately normal limits (table 5). These results lend

TABLE 5

THE BLOOD CHOLESTEROL DURING OEDEMA AND AFTER ITS SUBSIDENCE

CASE NO.	DATE	CHOLESTEROL MGM. PER CENT.	WEIGHT IN KGM.	OEDEMA
23	29·11	93·1	24·0	+
	12·12	124·1	20·0	—
25	29·7	105·7	25·2	+
	6·8	124·1	20·8	—
19	20·2	114·3	23·0	+
	28·2	120·7	20·6	—
11	27·2	102·5	14·2	+
	7·3	136·9	12·0	—
1	22·11	147·2	29·2	+ +
	3·12	131·0	24·2	—
17	3·4	157·4	23·8	+
	22·4	140·0	20·0	—
9	12·2	157·4	15·0	+
	19·2	136·9	12·5	—

support to the view that in nephritis the occurrence of hypercholesterolaemia and oedema is no more than a coincidence. Moreover, in oedema arising from certain other causes no increase in the blood cholesterol has been found. In a case of oedema associated with cardiac failure it was 93·1 mgm. per cent., in two cases of nutritional oedema 105·7 mgm. per cent. and in two infants with oedema of doubtful origin it was 90·2 mgm. per cent. and 58·6 mgm. per cent. respectively. In nephrosis on the other hand it is generally recognized that

oedema and hypercholesterolaemia go hand and hand. Three cases of the nephrotic syndrome have been observed for periods of several months and in all more or less parallel changes in the degree of oedema, as indicated by the body weight, and the cholesterol values were found. Estimations were made at frequent intervals and the results are shown in condensed form in table 6.

TABLE 6

THE BLOOD CHOLESTEROL IN NEPHROSIS

CASE NO.	DATE	CHOLESTEROL MGM. PER CENT.	WEIGHT IN KGM.
54	6.1.36	308·0	21·84
	8.2.36	579·0	23·0
	6.3.36	470·0	22·2
	22.5.36	299·0	18·2
55	2.3.36	214·9	27·8
	1.4.36	398·9	30·0
	8.5.36	444·8	30·8
	16.6.36	272·0	30·6
	7.7.36	260·0	29·6
	19.8.36	226·0	29·2
56	6.7.36	243·0	19·32
	6.8.36	255·0	19·28
	17.9.36	405·5	17·72
	7.10.36	164·3	15·6

Jaundice. Catarrhal jaundice appears to be an exception to the general rule that in febrile conditions the blood cholesterol is reduced. Serial estimations were made in ten children with this condition and in all there was increase in the blood cholesterol (table 7). In seven of the cases there was fever during the early stages and in five of them the blood cholesterol was over 170 mgm. per cent. As the jaundice decreased the cholesterol values fell. Three cases of congenital atresia of the bile ducts were examined and all showed high cholesterol values ranging from 140·9 to 204 mgm. per cent. (table 8). On the other hand, in uncomplicated haemolytic jaundice no increase in the blood cholesterol was found. In three cases of icterus gravis it ranged between 87·3 mgm. per cent. and 90·2 mgm. per cent. In a fourth case, however, in which there were signs of obstructive jaundice, probably due to blocking of bile capillaries with pigments, the blood cholesterol was 255·1 mgm. per cent. (table 9). In the one case of acholuric jaundice examined the cholesterol value was 75·9 mgm. per cent. It would appear, therefore, that in jaundice due to obstruction, even in the presence of fever, there is an increase in the blood cholesterol content, whereas in haemolytic jaundice the values tend to be low.

TABLE 7

THE BLOOD CHOLESTEROL IN CATARRHAL JAUNDICE

CASE	AGE IN YEARS	DATE	CHOLESTEROL MGM. PER CENT.	JAUNDICE
A. H.	6/12	11.8.36 1.9.36	251·0 111·5	+ —
M. L.	19/12	13.10.37 18.10.37	268·0 131.0	+ —
J. C.	2	4.1.36 14.1.36	255·1 111·5	+ —
G. B.	3	7.9.36 14.9.36	218·0 143·7	+ —
B. S.	5	6.10.36 19.10.36	160·8 143·7	+ —
S. McP.	5	18.3.36 31.3.36	197·0 127·6	++ —
J. S.	7	10.10.36	185·0	+
M. B.	7	8.11.37 29.11.37	164·3 133·9	++ ++
W. McG.	9	30.6.36 4.7.36	150·6 108·5	+ —
J. D.	11	23.2.37 6.3.37	143·7 105·7	+ —

TABLE 8

THE BLOOD CHOLESTEROL IN CONGENITAL ATRESIA OF THE BILE DUCTS

CASE NO.	NAME	AGE IN YEARS	CHOLESTEROL MGM. PER CENT.
23	A. L.	1/12	140·9
24	A. Y.	6/52	208·0
25	B.	2/52	193·1

TABLE 9

THE BLOOD CHOLESTEROL IN ICTERUS GRAVIS

CASE NO.	NAME	AGE IN YEARS	CHOLESTEROL MGM. PER CENT.	RESULT
43	A. B.	8/365	90·2	Died
44	R. P.	2/52	90·2	Died
45	O. D.	1/365	87·3	Died
46	D. B.	11/365	255·1	Recovered

Summary

In a group of healthy children the range of blood cholesterol content lay between 96 mgm. per cent. and 134 mgm. per cent. In pneumonia, empyema, acute rheumatic arthritis and in the early stages of acute nephritis the blood cholesterol content tended to be low and to rise with convalescence. Children suffering from a second or third attack of pneumonia showed low values. In nephrosis and obstructive jaundice high blood cholesterol values prevailed, whereas in oedema due to other causes and in haemolytic jaundice low values were frequently found.

Thanks are due to Professor G. B. Fleming and Professor Noah Morris for suggestions and much valuable advice and criticism. The expenses of this work were partly defrayed by a grant from the Medical Research Council.

REFERENCES.

Acũna, M., and Winoçur, P. (1931). *Arch. Méd. Enf.*, **34,** 409.
Baranski, R. (1926). *Ibid.*, **29,** 139.
Baylac, J., and Sendrail, M. (1928). *Ibid.*, **31,** 662.
Bloor, W. R. (1916). *J. biol. Chem.*, **24,** 447.
—— (1933). *Ibid.*, **103,** 699.
Blottner, H., and Fitz, R. (1934). *J. clin. Invest.*, **13,** 707.
—— (1935). *Arch. intern. Med.*, **55,** 121.
Callow, R. K., and Parkes, A. S. (1937). *Brit. med. J.*, **1,** 456.
Campbell, J. M. H. (1924). *Quart. J. Med.*, **18,** 123.
Chaikoff, I. L., McGavack, T. H., and Kaplan, A. (1934). *J. clin. Invest.*, **13,** 1.
Chauffard, A., Laroch, H., and Grigaut, A. (1920). *Ann. de Méd.*, **8,** 69.
Currie, A. N. (1924). *Brit. J. exp. Path.*, **5,** 293.
Denis, W. (1917). *J. biol. Chem.*, **29,** 93.
Gainsborough, H. (1935). *Proc. roy. Soc. Med.*, **28,** 989.
Gortz, S. (1937). *Acta Paediatr., Stockh.*, **19,** 553.
Goldbloom, A., and Gottlieb, R. (1927). *Canad. med. Ass. J.*, **17,** 1333.
Gordon, M. B., and Cohn, D. J. (1928). *Amer. J. Dis. Child.*, **35,** 193.
Grigaut, A. (1913). Thèse de Paris.
Kaiser, A. D., and Gray, M. S. (1934). *Amer. J. Dis. Child.*, **47,** 9.
Kipp, H. A. (1920). *J. biol. Chem.*, **44,** 215.
Leiboff, S. L. (1924). *Ibid.*, **61,** 177.
Lesné, E., Zizine, P., and Sylvestre, R. (1929). *Rev. franç. Pédiat.*, **5,** 423.
Manicatide, M., Bratesco, A., and Rusesco, R. (1927). *C. R. Soc. Biol., Paris*, **96,** 1240.
Maxwell, J. (1928). *Quart. J. Med.*, **21,** 297.
Molitch, M., and Poliakoff, S. (1936). *Arch. Pediat.*, **53,** 613.
Offenkrantz, F. M., and Karshan, M. (1936). *Amer. J. Dis. Child.*, **52,** 784.
Peters, J. P., and van Slyke, D.D. (1931). *Quantitative Clinical Chemistry, Interpretations*, London, 252.
Schube, P. G. (1937). *J. Lab. clin. Med.*, **22,** 280.
Simonini, A. (1933). *Clin. pediat., Modena*, **15,** 411.
Sperry, W. M. (1936*a*). *Amer. J. Dis. Child.*, **51,** 84.
—— (1936*b*). *J. biol. Chem.*, **114,** 125.
Steiner, A., and Turner, K. B. (1940). *J. clin. Invest.*, **19,** 373.

Stroesser, A. V. (1936). *Proc. Soc. exp. Biol., N.Y.*, **34,** 10.
Sylvestre, R. (1929). Thèse de Paris.
Teilum, G. (1935). *Acta med. scand.*, **85,** 316.
Vollmer, H. (1927). *Z. Kinderheilk.*, **44,** 87.
Ward, K. M. (1931). *Arch. Dis. Childh.*, **6,** 329.
Wilson, W. R., and Hanner, J. P. (1934). *J. biol. Chem.*, **106,** 323.

CASE REPORTS

ARACHNODACTYLY AND ECTOPIA LENTIS IN A FATHER AND DAUGHTER

BY

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For many years after the original description of ' dolichosténomélie ' by Marfan (1896), this peculiar type of local gigantism of the extremities received little general recognition until Ormond (1924, 1929) drew the attention of ophthalmologists to the frequent association of the skeletal deformities with congenital dislocation of the lenses.

Burch (1936), in a comprehensive review, was largely responsible for furthering recognition of the condition in America, and the number of cases that have been reported, mostly in the ophthalmological literature, during the past ten years is an indication that arachnodactyly is not of extreme rarity, and that many milder cases and ' formes frustes ' have previously passed unrecognized. Stewart (1939) considers that the condition is not uncommon amongst mental defectives, although the intelligence of reported cases has generally been described as normal. Most of the reports have appeared in the French and German literature, but cases have been described in this country by Poynton (1903), Thursfield (1920), Poynton and Maurice (1923), Ormond and Williams (1924), Cameron (1924), Fowler (1924), Young (1929), Ormond (1929, 1930), Ellis (1931), Hudson (1932), King (1934), Sorsby (1935), Cockayne (1935), and Stewart (1939).

As the name arachnodactyly (Achard, 1902) implies, the most striking feature of the condition is usually the extreme length and slenderness of the digits. The description is not universally applicable, however, since some cases, e.g. the first of those here reported, whilst clearly being mild examples of arachnodactyly, have the arms and legs principally affected, whilst the hands and feet are practically normal. The increased length of the extremities results in a characteristic build, the patients commonly being considerably above the average height, but so slender and with so little subcutaneous fat that the weight is often greatly below the normal. Deformities of the spine, particularly scoliosis and kyphosis, and of the thorax (pigeon-breast, Trichterbrust) are common. Laxity of the ligaments tends to make the patients clumsy and graceless, whilst deformities of the feet (pes planus, hammer-toe) are the general rule. Other bony abnormalities such as spina bifida (Brock, 1927; Zuber, 1928; Weill, 1932) have been described, whilst in three instances (Ellis, 1931; Semah, 1938; Boudet et al., 1939) arachnodactyly has been associated with fragilitas ossium and blue sclerotics.

In about two-thirds of the cases the skull is dolichocephalic. The orbital ridges have sometimes been described as prominent and the jaw as prognathous. The teeth may be normal or long and slender and the palate high and arched.

Radiologically the bones of the extremities, particularly the phalanges, metacarpals and metatarsals, show the extreme length and slenderness observed clinically. Ossification is usually normal for age; extra epiphyses have been described in the digits, but these do not appear to be the rule. Apart from dolichocephaly, the skull shows no characteristic changes, and the sella turcica is usually normal, though it may be reduced in size (Young, 1929). Weill (1932) found calcification in the region of the pineal in one instance.

Congenital morbus cordis occurs sufficiently often (in one-third or more of the cases) to be regarded as an integral part of the complete syndrome. It was present in the second of my cases.

Many other additional congenital abnormalities have been described, either in association with arachnodactyly or occurring in other members of affected families. Some degree of webbing of the fingers is common; the ears are often prominent or malformed; the musculature is poorly developed.

The incidence of respiratory infections appears unusually high, and a number of patients (Hudson, 1933; Piper and Irvine-Jones, 1926; Börger, 1914) have succumbed to pneumonia. It is of interest that in the two latter cases, in which post-mortem examination was performed, congenital abnormalities of the lungs were found. Severe asthma occurred in the second case here reported.

Congenital dislocation of the lenses, giving rise to tremulous irides ('iridodonesis'), small miotic pupils and occasionally to recurrent attacks of glaucoma, is found in approximately 50 per cent. of cases of arachnodactyly (Ormond, 1930). The dislocated lenses are often opaque (as in case 1) and resistant to absorption (Hudson, 1933).

The following two cases illustrate most of the clinical features of arachnodactyly, and its association with ectopia lentis.

Case reports

FAMILY HISTORY. The patients to be described are Stephen V., aged thirty-two years, and his daughter, Ruth V. aged four years. Neither Stephen V.'s parents nor he and his wife Ellen V. were blood relations. Stephen V.'s paternal grandfather is said to have been blind (cause unknown). Stephen V.'s father died in Pembury Hospital in 1940 from cardiac failure following hyperpiesia; his eyes and limbs were normal and at autopsy there was no evidence of congenital morbus cordis. Stephen V. has four brothers and two sisters; one brother suffers from defective sight (cause unknown), but is otherwise normal, the others being normal both as regards sight and build.

Ellen V., aged thirty-one years (wife of Stephen V. and mother of Ruth V.), has been blind from birth. The right eye shows interstitial keratitis and opacity of the lens, whilst on the left there is advanced syphilitic choroiditis and pallor of the optic nerve. The Wassermann and Kahn reactions are still strongly positive, although she has been under treatment for congenital syphilis since 1937. She suffers from migrainous headaches and has had epileptic attacks on several occasions. Her heart shows left-sided enlargement; there is a short presystolic murmur and a blowing systolic murmur in the mitral area. There

has only been one pregnancy (Ruth V.), during the latter months of which she suffered from oedema.

Case 1. Stephen V., aged thirty-two years, has been practically blind from birth. He was brought up in a blind school until the age of sixteen and was subsequently trained as a basket-maker. At the age of ten an unsuccessful operation on his right eye was performed at the Brighton Eye Hospital. He says that he learnt to walk late and ' was always falling about ' ; he was thought to be abnormally tall and thin during later childhood and adolescence. He has good general health, and apart from the limitations imposed by his eyesight is normally active.

On examination he is of striking build, being tall (6 ft. 2 in.) and exceptionally slender, the length of the arms and legs being particularly noticeable. He takes a size 14½ collar and all ready-made clothes are much too loose for him. The hands and feet, however, are not abnormal and he can wear size 8 shoes.

The skull is not abnormal, except for slight prominence of the orbital ridges and somewhat prognathous jaw. The teeth, particularly those of the upper jaw, are long, widely-spaced and project forward. The ears are also rather prominent.

There are no abnormalities of the spine, thorax, heart, lungs or abdomen. There is poor muscular development, and very little subcutaneous fat, though the patient is actually stronger than his appearance suggests.

EYES. There is bilateral iridodonesis. Both lenses are dislocated. On the right the lens lies one sixth within the pupil and is opaque; on the left the lens is two-thirds within the pupil and is semi-opaque. Unaided vision on the right is one-sixtieth and on the left two-sixtieths.

WASSERMANN and KAHN reactions negative.

Case 2. Ruth V., a girl, aged four years at the time of examination (May, 1940), was born four weeks prematurely weighing six and a half pounds; delivery was normal. The child was thought to be of unusual length at birth, and though she sucked and cried normally, she always appeared thin. She was fed on a cow's milk formula. At no time had she been cyanotic. An umbilical hernia was strapped for the first year.

At nine months of age the child developed pertussis, and at eleven months was admitted to Pembury County Hospital with infantile eczema. Recurrent asthmatic attacks, which have become more severe and frequent as she has got older, began during the second year. They have been associated with the gradual appearance of the thoracic deformity which she now shows. There is no known food or other idiosyncrasy, and the asthmatic attacks occur both in winter and in summer. The child has been admitted to hospital six times on account of asthma since 1937.

During the first year it was noted that the child did not see normally. She cut two teeth at three months of age and had sixteen teeth at a year old. She spoke words at eighteen months and began to walk at two years old. She is still very liable to fall over.

On examination (May, 1940). A tall, extremely slender child, who is active but ungainly and unsteady on her feet. Height 44¼ in. (normal for age 38 in.). Weight 35 pounds (normal for age 34 pounds, for height 45 pounds). Fig. 1 shows the characteristic length of the limbs and narrowness of the trunk, whilst the anxious expression of the face is also somewhat typical. The head measures 17·5 cm. in length and 12·5 cm. in breadth. The teeth are normal. The palate is high and arched. There is dorsal kyphosis and laxity of joint ligaments, particularly of the wrists, elbows and knees.

THE HANDS (fig. 2) measure 5¼ in. from the tip of the middle finger to the radial styloid (normal control 4½ in.), and show the typical ' spider fingers.'

FIG 1.—Ruth V., showing tall, slender build and deformity of thorax.

FIG. 2.—Ruth V.: Hands showing arachnodactyly.

THE FEET (fig. 3) are excessively long and slender. There is a hammer-toe deformity of the third and fourth toes on both sides.

THORAX. There is a well-marked pigeon-breast deformity of the chest, with flattening of the lower ribs anteriorly. Scattered wheezing expiratory râles are heard over both lungs.

HEART. The apex beat is palpable in the left fifth intercostal space immediately outside the nipple line, and the area of cardiac dullness extends half

an inch to the right of the right sternal border. There is a loud mid-diastolic murmur best heard at the apex, and also a harsh systolic murmur well heard in the third and fourth intercostal spaces immediately to the left of the sternum. The pulse rate is 100 to 110; there is a good response to exercise tolerance tests.

FIG. 3.—Ruth V.: Long, narrow feet and deformities of toes.

FIG. 4.—Ruth V.: Skiagraph of hands.

FIG. 5.—Ruth V.: Skiagraph of feet.

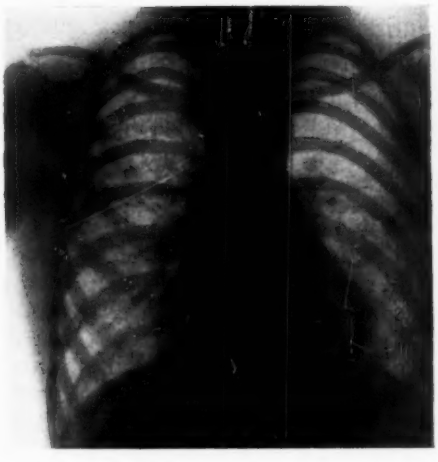

FIG. 6.—Ruth V.: Teleradiograph of heart, showing enlargement.

The orthodiagram confirms the cardiac enlargement, which is principally right-sided.

EYES. There is bilateral dislocation of the lens. The pupils dilate poorly, and there is bilateral iridodonesis. Visual tests show that acuity is moderately good.

MENTALITY. The child is mentally retarded, but educable, part at least of her backwardness being due to her prolonged hospitalization. She is moderately co-operative, understanding simple requests, and is beginning to speak in sentences. She is clean in habits.

The WASSERMANN and KAHN reactions and the MANTOUX TEST (1 in 1,000) are negative.

Discussion

The association of congenital abnormalities of the osseous system with congenital abnormalities of the eye is seen in other conditions than arachnodactyly. Examples are gargoylism (chondro-osteo-dystrophy and corneal opacities); congenital coloboma of the macula and apical dystrophy of hands and feet (Sorsby, 1935); punctate epiphyseal dysplasia associated with congenital cataract; and the Laurence-Moon-Biedl syndrome (polydactyly and retinitis pigmentosa, etc.). With the possible exception of punctate epiphyseal dysplasia, all these conditions may show a familial incidence and the ocular and osseous defects occur separately. In the case of the Laurence-Moon-Biedl syndrome, in which affected families have been studied in some detail, it has been suggested that a linkage of genes has taken place (Cockayne et al., 1935; Sorsby et al., 1939).

The two cases reported here illustrate the hereditary factor in both arachnodactyly and ectopia lentis, a 'forme fruste' of arachnodactyly with ectopia lentis in the father being followed by the appearance of the classical picture of arachnodactyly with ectopia lentis in the child. (The mother's blindness, though making the family a lamentable social phenomenon, is not regarded as being related to the condition in the child; there is no evidence that parental syphilis plays any part in the production of either arachnodactyly or ectopia lentis.) There was no consanguinity of the parents.

There are numerous reports in the literature in which arachnodactyly and ectopia lentis, combined or separately, have occurred in several siblings or in a parent and children. (Unfortunately few authors state whether or not there was consanguinity of the parents.)

Thus Achard (1902) described arachnodactyly in two sisters, their mother and maternal grandfather; Villard et al. (1931) reported a family consisting of a father (antecedents unknown) who suffered from ectopia lentis, a mother who was normal, and five children. Of the latter, the eldest boy and girl showed both arachnodactyly and ectopia lentis, a third child was normal, the fourth (a girl) had ectopia lentis only, and the fifth (a boy) was normal. Weve (1931) observed twenty-three cases of arachnodactyly in six families, in three of which there was certain evidence of hereditary transmission. The association of arachnodactyly and ectopia lentis was seen in a father, two sons, and a daughter. Weill (1932) observed both conditions in a mother and son, whilst in a second family the mother showed dislocation and calcification of the lenses associated with dwarfism, and her son ectopia lentis and a forme fruste of arachnodactyly. Young (1929) found arachnodactyly and associated congenital abnormalities in a mother, daughter and son. Harrison and Klainer (1939) give a family tree showing arachnodactyly in two siblings in one generation, and three in the next.

Although further familial studies are required definitely to establish the mode of inheritance and linkage of the two conditions, it seems probable that both arachnodactyly and ectopia lentis may be transmitted as Mendelian dominants, either separately or in association. There is no sex-linkage in either condition.

Thanks are due to Dr. W. C. Long, Honorary Radiologist to the Kent and

Sussex Hospital, for the skiagraphs, and to Dr. L. B. Langmead for the photographs.

References

Achard, C. (1902). *Bull. Soc. méd. Hôp. Paris*, **19**, 834.
Börger, F. (1914). *Z. Kinderheilk.*, **12**, 161.
Boudet, G., Balmès, J., and Barnay, J. (1939). *Bull. Soc. Pédiat. Paris.* **37**, 188.
Brock, J. (1927). *Klin. Wschr.*, **6**, 2289.
Burch, F. E. (1936). *Arch. Ophthal., N.Y.*, **15**, 645.
Cameron, H. C. (1924). *Proc. roy. Soc. Med.*, **17**, 32.
Cockayne, E. A. (1935). *Ibid.*, **29**, 120.
Cockayne, E. A., Krestin, D., and Sorsby, A. (1935). *Quart. J. Med.*, N.S., **4**, 93.
Ellis, R. W. B. (1931). *Proc. roy. Soc. Med.*, **24**, 54.
Fowler, J. S. (1924). *Guy's Hosp. Rep.*, **74**, 395 and 398.
Futcher, P. H., and Southworth, H. (1938). *Arch. intern. Med.*, **61**, 693.
Harrison, J., and Klainer, M. J. (1939). *New Engl. J. Med.*, **220**, 621.
Hudson, A. C. (1933). *Proc. roy. Soc. Med.*, **26**, 35.
King, E. F. (1934). *Ibid.*, **27**, 298.
Marfan, A. B. (1896). *Bull. Soc. méd. Hôp. Paris*, **13**, 220.
Ormond, A. W. (1929). *Int. ophthal. Congr.*, **2**, 645.
—— (1930). *Guy's Hosp. Rep.*, **80**, 68.
—— and Williams, R. G. (1924). *Ibid.*, **74**, 385.
Piper, R. K., and Irvine-Jones, E. (1926). *Amer. J. Dis. Child.*, **31**, 832.
Poynton, F. J. (1903). *Trans. med. Soc. Lond.*, **26**, 338.
—— and Maurice, W. B. (1923). *Ibid.*, **45**, 21.
Semah, F. (1938). *Riv. Clin. pediat.*, **36**, 228.
Sorsby, A. (1935). *Brit. J. Ophthal.*, **19**, 65.
—— Avery, H., and Cockayne, E. A. (1939). *Quart. J. Med.*, N. S., **8**, 51.
Stewart, R. M. (1939). *Arch. Dis. Childh.*, **14**, 64.
Thursfield, H. (1920). *St Bart.'s Hosp. med. Rep.*, **53**, 35.
Villard, H., Viallefont, H., and Temple, J. (1931). *Bull. Soc. Ophthal. Paris*, **46**, 384.
Weill, G. (1932). *Ann. Oculist.*, Paris, **169**, 21.
Weve, H. (1931). *Arch. Augenheilk.*, **104**, 1.
Young, M. L. (1929). *Arch. Dis. Childh.*, **4**, 190.
Zuber, A. (1928). *Bull Soc. Pédiat. Paris*, **26**, 311.

CONGENITAL CYST OF THE LARYNX CAUSING FATAL ASPHYXIA NEONATORUM

BY

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Congenital cysts in the region of the larynx of sufficient size to cause embarrassment of respiration at birth are rare, and the following case possesses several points of interest.

Case report

Baby S., the first child of young and perfectly healthy parents, was born after a normal pregnancy and confinement. A doctor was present at the delivery, and the child had apparently been quite all right immediately after birth. With the first respiration, however, it became cyanosed and made repeated attempts at a gasping type of respiration, finally passing into a state resembling asphyxia pallida. All possible immediate treatment was adopted; no mucus could be removed, and oxygen was obtained with little delay and administered by a nasal catheter. With continuous oxygen administration the condition of the child improved, but it remained limp, with frequent attacks of cyanosis and occasional convulsive gasps. As soon as the oxygen was diminished the child became visibly worse, and after about an hour and a half the doctor sent for my assistance, mentioning the symptoms, so that I took with me a further supply of oxygen and a small catheter for endotracheal use. I found the child in the state described above, and after ensuring that no mucus was obstructing the air passages, the possibility of a congenital abnormality was considered. It was unlikely that a tracheo-oesophageal fusion existed, as some air was evidently getting into the lungs, and the extent of the respiratory effort suggested that there was no gross failure of expansion of the lungs.

The back of the pharynx was inspected directly and digital palpation of the superior aperture of the larynx was achieved, but no abnormalities were found. We were successful in passing a nasal catheter even into the trachea, and it was concluded that the case must be one of cerebral trauma. Arrangements for a nurse to tend the child were made, and it was suggested that if no improvement took place in a few hours the child should be transferred to the hospital for better supervision. Two hours later, as it was no better, the child was sent into the North Middlesex Hospital, but became worse in transit, with increased cyanosis, and on admission it was moribund and died before I was able to see it again.

Post-mortem examination revealed the cause of the trouble : a thin-walled cyst, containing fluid and about 2·5 cm. in diameter, lay over the superior aperture of the larynx, acting as a ball-valve.

It arose from the mucous membrane of the left recessus piriformis immediately below the aryepiglottic fold. At birth it probably lay in the recess, but its attachment to the mucosa was sufficiently loose to allow of its being drawn over the superior aperture of the larynx, probably with the first breath of the infant, effectively blocking air entry. Being thin-walled and not unduly tense, it had escaped the examining finger, and allowed the entrance of a catheter beside it; even the entrance of oxygen into the pharynx and larynx would diminish the tendency for violent inspiratory effort and make the valve action less pronounced. As soon as oxygen was cut off the next deep breath sucked it in again. Death was probably due ultimately to exhaustion, as a degree of trauma had been unavoidable in the several examinations of the infant.

The accompanying photograph illustrates the condition. The specimen was removed to the museum of the Royal College of Surgeons to be fixed before the wall was sectioned. The war has intervened and interrupted the investi-

FIG. 1.

gation of its structure, but its external appearances, with a thin wall, leave little doubt that the lining consists of a thin layer of flattened cells. It was apparent that it was confined to the mucous membrane of the outer part of the larynx and was not connected with the deep tissues, so that a branchial cleft origin is practically ruled out, and it is likely that the condition is one of simple retention cyst of a mucous gland. There is no possibility of an aerocele as a basis.

No other cysts or other abnormalities of the larynx or elsewhere were found. The lungs showed partial expansion, with a few areas of atelectasis.

Discussion

The rarity of congenital cysts of the larynx is shown by the fact that Jacobi and Roscoff (1935) in a thorough search of the literature were only able to collect eleven cases, to which they added two of their own. They mention several possible sources for such cysts: the commonest is probably closure of a mucous gland, but this is not likely to occur until after birth, though it is possible that during intra-uterine swallowing of liquor a fragment of debris may block a gland. Other possibilities are inclusions of epithelial cells, dermoids and distension of blood and lymph channels. Park and Israel (1925) suggest that birth trauma may be a factor. Tow (1937) mentions the work of Jacobi and Roscoff and also refers to cases reported by Lorie and Lux, and by Chamberlain. In the series described by Jacobi and Roscoff eleven were noted at birth, one on the second day and one in the third week. Asphyxial signs were present in all, though not always at birth, and four cases recovered either following operation or after spontaneous rupture of the cyst. In most cases the cysts were multiple, and were visible externally as bulges in the neck. The cysts varied in position, the epiglottis, right laryngo-epiglottic fold, the laryngeal wall and the deep tissues of the neck being mentioned as sites. The cause of the respiratory embarrassment was usually direct pressure on the larynx by the cystic mass, and in no case was a ball-valve effect described.

In only one case was the cyst in the site of the one described here, and in that one case the cysts were multiple. Diagnosis was made in most cases by the presence of a swelling in the neck, with in several cases direct laryngoscopic confirmation of the condition.

In the present case there was little opportunity for laryngoscopy and the child died before operative interference could be attempted. If the cyst had been palpated, it is possible that puncture might have been attempted. The cures reported have been the result of somewhat extensive operative interference in infants who survived the immediate respiratory embarrassment, or in whom the symptoms did not become severe until some months after birth; in one case a partial laryngectomy was carried out after preliminary tracheotomy in a five months old child, and in another case the cyst was perforated and did not recur.

Summary

A case is described of congenital laryngeal cyst causing asphyxia neonatorum. Diagnosis was not achieved during life.

It is shown that such cases are rare, and that, in fact, no similar valve effect of a single cyst appears to have been described.

Though rare, it is worth considering in a case of puzzling neonatal asphyxia whether a laryngeal cyst might be present, as, if diagnosed, a cure is possible.

Thanks are due to Mr. Ivor Lewis, medical superintendent of the North Middlesex Hospital for permission to publish this case.

References

Jacobi, M., and Roscoff, H. (1935). *Amer. J. Dis. Child.*, **49**, 448.
Park, J. H., and Israel, S. (1925). *Sth. med. J., Birmingham*, **18**, 128.
Tow, A. (1937). *Diseases of the New Born*, Oxford.

VOLVULUS IN A THREE-WEEKS-OLD BABY WITH A MECKEL'S DIVERTICULUM AND CONGENITAL MORBUS CORDIS

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Volvulus is a comparatively rare occurrence in childhood and in infancy is of extreme rarity. Occasional cases of foetal volvulus have been described, due to extension of the normal umbilical cord torsion to the intestine, to anomalies of the mesenteric attachment, to fixation of the bowel through a Meckel's diverticulum, or through peritoneal bands. It may be a terminal phenomenon in congenital atresia of the bowel, and in one such case described by Saxl in 1930, the infant was born alive and developed characteristic signs and symptoms of obstruction on the second day of life. At autopsy there was found a volvulus, due to congenital atresia of the ileum and to a common mesentery, and also a band between the gall bladder and the appendix. In addition the infant had a congenital cardiac lesion, a patent ductus arteriosus.

Case report

The case here recorded was a female infant, the ninth child of a mother aged forty-three, born prematurely by breech presentation, and weighing 4 lb. 7 oz. She had mongoloid features but otherwise appeared a normal thirty-three weeks gestation baby. The cord separated on the sixth day, at which time she weighed 4 lb. Because of the failure of the mother's milk she was given feeds of lactic acid milk with 10 per cent. glucose, one ounce two hourly, and on this formula she did well, regaining her birth weight by the twentieth day. Ext. thyroid sicc. $\frac{1}{10}$ grain, b.d., was added from the tenth day. She had occasional attacks of cyanosis, thought to be due to atelectasis, which responded to carbon dioxide and oxygen. The heart sounds were normal. There was no vomiting, and the stools were normal.

On the twenty-first day, fever (T. 104° F.) and dyspnoea developed and she presented the picture of broncho-pneumonia, with scattered patches of bronchial breathing over both bases.

The next day she became rapidly worse and died. About three hours before death she manifested symptoms of shock and sudden collapse, and her abdomen distended, but there was no vomiting, and her stools remained normal.

Post-mortem examination was made by Dr. W. Whitelaw, the hospital pathologist, seven hours after death, and his report was as follows :—

The body of a premature female infant, with mongoloid facies, and markedly protuberant abdomen. Weight 4 lb. 9 oz.

THORAX. The heart is enlarged and there is a wide defect in the interventricular septum. The aortic and pulmonary vessels are normal, the ductus arteriosus closed and the foramen ovale well valved.

The lungs show scattered areas of atelectasis at both bases but no broncho-pneumonia.

ABDOMEN. On opening the abdomen a small quantity of blood-stained fluid is noticed. The small bowel is distended to a distance about twelve inches above the caecum at which point a volvulus has occurred. The bowel between this point (which shows the presence of a Meckel's diverticulum, free from any adhesions or fixation, about half an inch in diameter) and the ileocaecal valve, is plum-coloured and contains blood. The twist of the strangulated bowel is a half turn counter-clockwise. The mesentery is unusually long, but otherwise normal. The peritoneal coat over the affected bowel still retains its lustre, pointing to the very recent onset of the obstruction. The appendix and caecum are unaltered, and the large bowel contains normal faeces. The stomach and duodenum are normal.

The following points are of interest :—

1. The only sign of volvulus was the sudden abdominal distension. There was no vomiting and the stools were normal.

2. Apart from a long mesentery, the only causative factor of the volvulus found was a Meckel's diverticulum, yet this was quite free from any fixation.

3. Congenital morbus cordis is a frequent finding in mongols ; although this infant was the ninth child of an elderly mother she had no other signs of mongolism except the facies.

Saxl's case, referred to above, which was not a mongol, also had a congenital cardiac lesion.

Thanks are due to Dr. T. M. Anderson, Medical Superintendent of the Hospital, for permission to publish this case, and to Dr. Whitelaw for the post-mortem findings.

REFERENCE

Saxl, N. J. (1930). *Amer. Med.*, **36**, 706.